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Attorneys for Defendant and Counterclaimant
SENORX, INC.

IN THE UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN JOSE DIVISION

HOLOGIC, INC., CYTYC CORPORATION and HOLOGIC L.P.,

Plaintiffs,

v.

SENORX, INC.,

Defendant.

SENORX, INC.,

Counterclaimant,

v.

HOLOGIC, INC., CYTYC CORPORATION and HOLOGIC L.P.,

Counterdefendants.

Case No. 08-CV-0133 RMW

DECLARATION OF AARON P. MAURER IN SUPPORT OF DEFENDANT SENORX, INC.'S OPPOSITION TO PLAINTIFFS' MOTION FOR A PRELIMINARY INJUNCTION

Date: April 21, 2008
Time: 2:00 p.m.
Courtroom: 6, 4th Floor
Judge: Hon. Ronald M. Whyte

I, Aaron P. Maurer, declare that I am a Partner at the law firm of Williams & Connolly LLP, and outside counsel for Defendant and Counterclaimant SenoRx, Inc. in the above-captioned matter. The following declaration is based on my personal knowledge, and if called to testify I could and would competently testify as to the matters set forth herein.

1. Attached hereto as Exhibit 1 is a true and correct copy of relevant excerpts of the transcript of the Deposition of Glenn Magnuson (March 18, 2008).

2. Attached hereto as Exhibit 2 is a true and correct copy of an excerpt of the Tenth Edition of Miriam Webster's Collegiate Dictionary, containing the definition of "lumen."

3. Attached hereto as Exhibit 3 is a true and correct copy of the Claim Construction Order (Docket No. 109), from the case captioned Xoft, Inc. v. Cytyc Corp., et al., Case Number C-05-05312 RMW, in the United States District Court for the Northern District of California.

4. Attached hereto as Exhibit 4 is a true and correct copy of U.S. Patent Number 6,413,204.

5. Attached hereto as Exhibit 5 is a true and correct copy of R.D. Ashpole et al., *A New Technique of Brachytherapy for Malignant Gliomas with Caesium-137: A New Method Utilizing a Remote Afterloading System*, Clinical Oncology 2:333-337 (1990).

6. Attached hereto as Exhibit 6 is a true and correct copy of U.S. Patent Number 6,482,142.

7. Attached hereto as Exhibit 7 is a true and correct copy of Plaintiffs' Objections and Responses to SenoRx's First Set of Interrogatories (Nos. 1-4).

8. Attached hereto as Exhibit 8 is a true and correct copy of Cytyc Corporation's (and Hologic's predecessor Proxima Therapeutics') Opening Claim Construction Brief (Docket No. 48), from the case captioned Xoft, Inc. v. Cytyc Corp., et al., Case Number C-05-05312 RMW, in the United States District Court for the Northern District of California.

9. Attached hereto as Exhibit 9 is a true and correct copy of the Patent Application for U.S. Patent Number 6,482,142.

10. Attached hereto as Exhibit 10 is a true and correct copy of an Office Action from the Patent Prosecution History for U.S. Patent Number 6,482,142.

11. Attached hereto as Exhibit 11 is a true and correct copy of U.S. Patent Number 6,036,631.

12. Attached hereto as Exhibit 12 is a true and correct copy of a Response to an Office Action from the Patent Prosecution History for U.S. Patent Number 6,482,142.

13. Attached hereto as Exhibit 13 is a true and correct copy of U.S. Patent Number 5,931,774.

14. Attached hereto as Exhibit 14 is a true and correct copy of relevant excerpts of SenoRx, Inc.'s 510(k) Submission for the SenoRad Multi-Lumen Balloon Source Applicator for Brachytherapy.

15. Attached hereto as Exhibit 15 is a true and correct copy of the Instruction Manual for the MammoSite Radiation Therapy System.

16. Attached hereto as Exhibit 16 is a true and correct copy of relevant excerpts of Protocol Number S07-002 for "A Multi-Site Prospective, Non Randomized Study Utilizing the Contura™ Multi-Lumen Balloon (MLB) Breast Brachytherapy Applicator to Deliver Accelerated Partial Breast Irradiation: Analysis of Dosimetric Success, Local Tumor Control, Cosmetic Outcome, Acute and Chronic Toxicity, and Clinical Scenarios for Optimal Use" (March 6, 2008).

17. Attached hereto as Exhibit 17 is a true and correct copy of the Settlement Agreement, License, and Mutual Release among the parties in the case captioned Xoft, Inc. v. Cytyc Corp., et al., Case Number C-05-05312 RMW, in the United States District Court for the Northern District of California.

18. Attached hereto as Exhibit 18 is a true and correct copy of relevant excerpts of the Memorandum of Points and Authorities in Support of Cytyc's Opposition to Xoft, Inc.'s Motion to Compel a Further Deposition of James Stubbs and, to Produce Documents without Objection (Docket No. 133), from the case captioned Xoft, Inc. v. Cytyc Corp., et al., Case Number C-05-05312 RMW, in the United States District Court for the Northern District of California.

19. Attached hereto as Exhibit 19 is a true and correct copy of relevant excerpts of the Form 10-K SEC filing for Hologic, Inc., filed November 27, 2007.

20. Attached hereto as Exhibit 20 is a true and correct copy of a document titled "Competitive Evaluation February 2008."

21. Attached hereto as Exhibit 21 is a true and correct copy of a document titled "Competition: How Does it Affect Me??"

22. Attached hereto as Exhibit 22 is a true and correct copy of a document titled "2008 MammoSite Strategic Plan," dated September 12, 2007.

23. Attached hereto as Exhibit 23 is a true and correct copy of a document titled "Competition Q2 Update."

24. Attached hereto as Exhibit 24 is a true and correct copy of a document titled "MammoSite Competitive Update," dated May 2007.

25. Attached hereto as Exhibit 25 is a true and correct copy of a document titled "Competition."

26. Attached hereto as Exhibit 26 is a true and correct copy of relevant excerpts of the MammoSite Strategic Plan (October 12, 2006).

27. Attached hereto as Exhibit 27 is a true and correct copy of the Contura™ Multi-Lumen Balloon Source Applicator for Brachytherapy Instructions for Use.

28. Attached hereto as Exhibit 28 is a true and correct copy of relevant excerpts of a presentation from SenoRx, Inc.'s September 27, 2007, Board of Directors' Meeting.

29. Attached hereto as Exhibit 29 is a true and correct copy of relevant excerpts of the Form 10-Q/A SEC filing for Hologic, Inc., filed February 12, 2008.

30. Attached hereto as Exhibit 30 is a true and correct copy of a presentation titled "SenoRx Initial Public Offering (NASDAQ: SENO)," dated March 2007.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: March 28, 2008

/s/
Aaron P. Maurer

ATTESTATION UNDER GENERAL ORDER NO. 45, § X.B.

As required by General Order No. 45, § X.B., I hereby attest that concurrence in the filing of the document has been obtained from the other signatory to the Declaration of Aaron P. Maurer in Support of Defendant SenoRx, Inc.'s Opposition to Plaintiffs' Motion for Preliminary Injunction.

Dated: March 28, 2008

By: s/F.T. Alexandra Mahaney
F.T. Alexandra Mahaney
amahaney@wsgr.com

CERTIFICATE OF SERVICE
U.S. District Court, Northern District of California,
Hologic, Inc. et al. v. SenoRx, Inc.
Case No. C-08-0133 RMW (RS)

I, Kirsten Blue, declare:

I am and was at the time of the service mentioned in this declaration, employed in the County of San Diego, California. I am over the age of 18 years and not a party to the within action. My business address is 12235 El Camino Real, Ste. 200, San Diego, CA, 92130.

On March 28, 2008, I served a copy(ies) of the following document(s):

DECLARATION OF AARON P. MAURER IN SUPPORT OF DEFENDANT SENORX, INC.'S OPPOSITION TO PLAINTIFFS' MOTION FOR A PRELIMINARY INJUNCTION

on the parties to this action by placing them in a sealed envelope(s) addressed as follows:

Henry C. Su (suh@howrey.com) Katharine L. Altemus (altemusk@howrey.com) HOWREY LLP 1950 University Avenue, 4th Floor East Palo Alto, CA 94303 Telephone: (650) 798-3500 Facsimile: (650) 798-3600	Attorneys for Plaintiffs HOLOGIC, INC. CYTYC CORPORATION and HOLOGIC LP
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☒ (BY ELECTRONIC MAIL) I caused such document(s) to be sent via electronic mail (email) to the above listed names and email addresses.

☒ (BY CM/ECF) I caused such document(s) to be sent via electronic mail through the Case Management/Electronic Case File system with the U.S. District Court for the Northern District of California.

I declare under penalty of perjury under the laws of the United States that the above is true and correct, and that this declaration was executed on March 28, 2008.

Kirsten Blue

Exhibit 2


Merriam
Webster's
Collegiate
Dictionary
TENTH EDITION

Merriam-Webster's Collegiate® Dictionary

TENTH EDITION

Merriam-Webster, Incorporated
Springfield, Massachusetts, U.S.A.

A GENUINE MERRIAM-WEBSTER

The name *Webster* alone is no guarantee of excellence. It is used by a number of publishers and may serve mainly to mislead an unwary buyer.

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1. English language—Dictionaries. I. Merriam-Webster, Inc.

PE1628.M36 1996

423—dc20 95-36076

CIP

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Made in the United States of America

1516RMcN96

one of reducing friction, heat, and wear when introduced as a film between solid surfaces 2 : something that lessens or prevents friction or difficulty — **lubricant** *adj*

lu-bri-cate \'lü-brə-ˌkāt\ *vb* **-cat-ed; -cat-ing** [L *lubricatus*, pp. of *lubricare*, fr. *lubricus* slippery — more at SLEEVE] *vt* (ca. 1623) 1 : to make smooth or slippery 2 : to apply a lubricant to ~ *vi* : to act as a lubricant — **lu-bri-ca-tion** \ˌlü-brə-ˈkā-shən\ *n* — **lu-bri-ca-tive** \'lü-brə-ˌkā-tiv\ *adj* — **lu-bri-ca-tor** \-ˌkā-tər\ *n*

lu-bri-cious \lü-'bri-shəs\ *or* **lu-bri-ceous** \'lü-bri-kəs\ *adj* [ML *lubricus*, fr. L, slippery, easily led astray] (1535) 1 : marked by wantonness : LECHEROUS; *also* : SALACIOUS 2 [L *lubricus*] : having a smooth or slippery quality (a ~ skin) — **lu-bri-cious-ly** *adv*

lu-bric-i-ty \lü-'bri-sə-tē\ *n, pl* **-ties** (15c) : the property or state of being lubricious; *also* : the capacity for reducing friction

Lu-can \'lü-kən\ *adj* [LL *lucanus*, fr. *Lucas* Luke, fr. Gk *Loukas*] (1890) : of or relating to Luke or the Gospel ascribed to him

lu-carne \lü-'kärn\ *n* [F] (ca. 1825) : DORMER

Lu-ca-yo \lü-'kī-(ˌ)ō\ *also* **Lu-ca-yan** \-'kī-ən\ *n* (1929) : a member of an Arawakan people of the Bahamas

lu-cen-cy \'lü-s'n(t)-sē\ *n* (1656) : the quality or state of being lucent — more at LIGHT]

lu-cent \'lü-s'nt\ *adj* [ME, fr. L *lucent-, lucens*, prp. of *lucēre* to shine] (15c) 1 : glowing with light : LUMINOUS 2 : marked by clarity or translucence : CLEAR — **lu-cent-ly** *adv*

lu-cern *n* [prob. modif. of G *lüchsern* of a lynx, fr. *Luchs* lynx] (ca. 1533) *obs* : LYNX

lu-cerne *also* **lu-cern** \lü-'sərn\ *n* [F *luzerne*, fr. Prov *luserno*] (1626) *chiefly Brit* : ALFALFA

lu-cid \'lü-səd\ *adj* [L *lucidus*, fr. *lucēre*] (1591) 1 a : suffused with light : LUMINOUS b : TRANSLUCENT 2 : having full use of one's faculties : SANE 3 : clear to the understanding : INTELLIGIBLE *syn* see CLEAR — **lu-cid-ly** *adv* — **lu-cid-ness** *n*

lu-cid-i-ty \lü-'si-də-tē\ *n* (1851) 1 : clearness of thought or style 2 : a presumed capacity to perceive the truth directly and instantaneously : CLAIRVOYANCE

Lu-ci-fer \'lü-sə-fər\ *n* [ME, the morning star, a fallen rebel archangel, the Devil, fr. OE, fr. L, the morning star, fr. *lucifer* light-bearing, fr. *luc-, lux* light + *-fer* -ferous — more at LIGHT] (bef. 12c) 1 — used as a name of the devil 2 : the planet Venus when appearing as the morning star 3 *not cap* : a friction match having as active substances antimony sulfide and potassium chlorate — **Lu-ci-fe-ri-an** \ˌlü-sə-'fir-ē-ən\ *adj*

lu-cif-er-ase \lü-'si-fə-ˌrās, -ˌrāz\ *n* [ISV, fr. *luciferin*] (1888) : an enzyme that catalyzes the oxidation of luciferin

lu-cif-er-in \-f(ə-)rən\ *n* [ISV, fr. L *lucifer* light-bearing] (1888) : any of various organic substances in luminescent organisms (as fireflies) that upon oxidation produce a virtually heatless light

lu-cif-er-ous \lü-'si-f(ə-)rəs\ *adj* [L *lucifer*] (1648) : bringing light or insight : ILLUMINATING

Lu-ci-na \lü-'sī-nə\ *n* [L, Roman goddess of childbirth] (1658) *archaic* : MIDWIFE

Lu-cite \'lü-ˌsīt\ *trademark* — used for an acrylic resin or plastic consisting essentially of polymerized methyl methacrylate

luck \'lək\ *n* [ME *lucke*, fr. MD *luc*; akin to MHG *gelücke* luck] (15c) 1 a : a force that brings good fortune or adversity b : the events or circumstances that operate for or against an individual 2 : favoring chance; *also* : SUCCESS — **luck-less** \-ləs\ *adj*

luck *vi* (ca. 1584) 1 : to prosper or succeed esp. through chance or good fortune — usu. used with *out* 2 : to come upon something desirable by chance — usu. used with *out, on, onto*, or *into*

luck-i-ly \'lə-kə-lē\ *adv* (1530) 1 : in a lucky manner 2 : FORTUNATELY 2 (~, we were on time) *usage* see HOPEFULLY

lucky \'lə-kē\ *adj* **luck-i-er; -est** (15c) 1 : having good luck 2 : happening by chance : FORTUITOUS 3 : producing or resulting in good by chance : FAVORABLE 4 : seeming to bring good luck (a ~ rabbit's foot) — **luck-i-ness** \'lə-kē-nəs\ *n*

syn LUCKY, FORTUNATE, HAPPY, PROVIDENTIAL mean meeting with unforeseen success. LUCKY stresses the agency of chance in bringing about a favorable result (won because of a *lucky* bounce). FORTUNATE suggests being rewarded beyond one's deserts (*fortunate* in my investments). HAPPY combines the implications of LUCKY and FORTUNATE with stress on being blessed (a series of *happy* accidents). PROVIDENTIAL more definitely implies the help or intervention of a higher power (a *providential* change in the weather).

lucky dip *n* (1925) *Brit* : GRAB BAG

lu-cra-tive \'lü-krə-tiv\ *adj* [ME *lucratif*, fr. MF, fr. L *lucrativus*, fr. *lucratus*, pp. of *lucrari* to gain, fr. *lucrum*] (15c) : producing wealth : PROFITABLE — **lu-cra-tive-ly** *adv* — **lu-cra-tive-ness** *n*

lu-cre \'lü-kər\ *n* [ME, fr. L *lucrum*; prob. akin to OE *lēan* reward, OHG *lōn*, Gk *apolauein* to enjoy] (14c) : monetary gain : PROFIT; *also* : MONEY

lu-cu-bra-tion \ˌlü-kyə-'brā-shən, ˌlü-kə-\ *n* [L *lucubration-, lucubratio*] study by night, work produced at night, fr. *lucubrare* to work by lamplight; akin to L *luc-, lux*] (1595) : laborious or intensive study; *also* : the product of such study — usu. used in pl.

lu-cu-lent \'lü-kyə-lənt\ *adj* [L *luculentus*, fr. *luc-, lux* light] (ca. 1548) : clear in thought or expression : LUCID — **lu-cu-lent-ly** *adv*

Lu-cul-lan \lü-'kə-lən\ *also* **Lu-cul-li-an** \-'kə-lē-ən\ *adj* [L *luculllanus* of Licinius *Lucullus*; fr. his reputation for luxurious banquets] (1861) : LAVISH, LUXURIOUS (a ~ feast)

Ludd-ite \'lə-ˌdīt\ *n* [perh. fr. Ned *Ludd*, 18th cent. Leicestershire workman who destroyed machinery] (1811) : one of a group of early 19th century English workmen destroying laborsaving machinery as a protest; *broadly* : one who is opposed to esp. technological change — **Luddite** *adj*

lu-dic \'lü-dik\ *adj* [F *ludique*, fr. L *ludus*] (1940) : of, relating to, or characterized by play : PLAYFUL (~ behavior) (a ~ novel)

lu-di-crous \'lü-də-krəs\ *adj* [L *ludicrus*, fr. *ludus* play, sport; perh. akin to Gk *loidoros* abusive] (1782) 1 : amusing or laughable through obvious absurdity, incongruity, exaggeration, or eccentricity 2 : meriting derisive laughter or scorn as absurdly inept, false, or foolish *syn* see LAUGHABLE — **lu-di-crous-ly** *adv* — **lu-di-crous-ness** *n*

lu-es \'lü-(ˌ)ēz\ *n, pl* **lues** [NL, fr. L, plague; akin to Gk *lyein* to loosen, destroy — more at LOSE] (1634) : SYPHILIS — **lu-et-ic** \lü-'e-tik\ *adj*

luff \'ləf\ *n* [ME, weather side of a ship, luff, fr. MF *lof* weather side of ship] (14c) 1 : the act of sailing a ship nearer the wind 2 : the forward edge of a fore-and-aft sail

luff *vi* (14c) : to turn the head of a ship toward the wind

luf-fa *var of* LOOFAH

luft-mensch \'lüft-ˌmen(t)sh\ *n, pl* **luft-mensch-en** \-ˌmen(t)-shən\ [Yiddish *luftmentsh*, fr. *luft* air + *mentsh* human being] (1907) : an impractical contemplative person having no definite business or income

lug \'ləg\ *vb* **lugged; lug-ging** [ME *luggen* to pull by the hair; akin to Norw *lugga* to pull by the hair] (14c) 1 : DRAG, PULL 2 : to carry laboriously 3 : to introduce in a forced manner (~s my name into the argument) ~ *vi* 1 : to pull with effort : TUG 2 : to move heavily or by jerks (the car ~s on hills) 3 *of a racehorse* : to swerve from the course toward or away from the inside rail

lug *n* (1616) 1 *archaic* a : an act of lugging b : something that is lugged c : a shipping container for produce 2 : LUGSAIL 3 *pl* : superior airs or affectations (put on ~s) 4 *slang* : an exaction of money — used in the phrase *put the lug on*

lug *n* [ME (Sc) *lugge*, perh. fr. ME *luggen*] (15c) 1 : something (as a handle) that projects like an ear: as a : a leather loop on a harness saddle through which the shaft passes b : a metal fitting to which electrical wires are soldered or connected 2 *chiefly Brit* : EAR 3 : a ridge (as on the bottom of a shoe) to increase traction 4 : a nut used to secure a wheel on an automotive vehicle — called also *lug nut* 5 : BLOCKHEAD, LOUT

Lu-gan-da \lü-'gän-də, -'gan-\ *n* (1889) : the Bantu language of the Ganda people

luge \'lüzh\ *n* [F] (1905) : a small sled that is ridden in a supine position and used esp. in competition; *also* : the competition itself — **luge** *vi* — **lug-er** \'lü-zhər\ *n*

lug-gage \'lə-gij\ *n* (1596) : something that is lugged; *esp* : suitcases for a traveler's belongings : BAGGAGE

lug-ger \'lə-gər\ *n* [*lugsail*] (1757) : a small fishing or coasting boat that carries one or more lugsails

lug-sail \'ləg-ˌsāl, -səl\ *n* [perh. fr. *'lug*] (1677) : a 4-sided sail bent to an obliquely hanging yard that is hoisted and lowered with the sail

lu-gu-bri-ous \lü-'gü-brē-əs *also* -'gyü-\ *adj* [L *lugubris*, fr. *lugēre* to mourn; akin to Gk *lygros* mournful] (1601) 1 : MOURNFUL; esp : exaggeratedly or affectedly mournful (dark, dramatic and ~ brooding —S. Pritchett) 2 : DISMAL (a ~ landscape) — **lu-gu-bri-ous-ly** *adv* — **lu-gu-bri-ous-ness** *n*

lug-worm \'ləg-ˌwərm\ *n* [origin unknown] (1802) : any of a genus (*Arenicola*) of marine polychaete worms that have a row of tufted gills along each side of the back and are used for bait

Luk-an \'lü-kən\ *var of* LUCAN

Luke \'lük\ *n* [L *Lucas*, fr. Gk *Loukas*] 1 : a Gentile physician and companion of the apostle Paul traditionally identified as the author of the third Gospel in the New Testament and of the book of Acts 2 : the third Gospel in the New Testament — see BIBLE table

luke-warm \'lük-'wȯrm\ *adj* [ME, fr. *luke* lukewarm + *warm*; prob. akin to OHG *lāo* lukewarm — more at LEE] (14c) 1 : moderately warm : TEPID 2 : lacking conviction : HALFHEARTED — **luke-warm-ly** *adv* — **luke-warm-ness** *n*

lull \'ləl\ *vt* [ME; prob. of imit. origin] (14c) 1 : to cause to sleep or rest : SOOTHE 2 : to cause to relax vigilance

lull *n* (1719) 1 *archaic* : something that lulls; *esp* : LULLABY 2 : a temporary pause or decline in activity (the early morning ~ in urban noise): as a : a temporary calm before or during a storm b : a temporary drop in business activity

lul-la-by \'lə-lə-ˌbī\ *n, pl* **-bies** [obs. E *lulla*, interj. used to lull a child (fr. ME) + *bye*, interj. used to lull a child. fr. ME *by*] (1588) : a soothing refrain; *specif* : a song to quiet children or lull them to sleep

lullaby *vt* **-bied; -by-ing** (1592) : to quiet with or as if with a lullaby

lu-lu \'lü-(ˌ)lü\ *n* [prob. fr. *Lulu*, nickname fr. *Louise*] (1886) *slang* : one that is remarkable or wonderful

lum \'ləm\ *n* [origin unknown] (ca. 1628) *chiefly Scot* : CHIMNEY

lum-ba-go \ˌləm-'bā-(ˌ)gō\ *n* [L, fr. *lumbus*] (ca. 1693) : usu. painful muscular rheumatism involving the lumbar region

lum-bar \'ləm-bər, -ˌbär\ *adj* [NL *lumbaris*, fr. L *lumbus* loin — more at LOIN] (ca. 1656) : of, relating to, or constituting the loins or the vertebrae between the thoracic vertebrae and sacrum (~ region)

lum-ber \'ləm-bər\ *vi* **lum-bered; lum-ber-ing** \-b(ə-)riŋ\ [ME *lomeren*] (14c) 1 : to move ponderously 2 : RUMBLE

lumber *n* [perh. fr. *Lombard*; fr. the use of pawnshops as storehouses of disused property] (1552) 1 : surplus or disused articles (as furniture) that are stored away 2 a : timber or logs esp. when dressed for use b : any of various structural materials prepared in a form similar to lumber — **lumber** *adj*

lumber *vb* **lum-bered; lum-ber-ing** \-b(ə-)riŋ\ *vt* (1642) 1 : to clutter with or as if with lumber : ENCUMBER 2 : to heap together in disorder 3 : to log and saw the timber of ~ *vi* 1 : to cut logs for lumber 2 : to saw logs into lumber for the market — **lum-ber-er** \-bər-ər\ *n*

lum-ber-jack \'ləm-bər-ˌjak\ *n* (1831) : LOGGER

lum-ber-man \-mən\ *n* (ca. 1817) : a person who is engaged in or oversees the business of cutting, processing, and marketing lumber

lumber room *n* (1741) : STOREROOM

lum-ber-yard \-ˌyärd\ *n* (1786) : a yard where a stock of lumber is kept for sale

lum-bo-sa-cral \ˌləm-bō-'sā-krəl, -'sā-\ *adj* (1840) : relating to the lumbar and sacral regions or parts

lu-men \'lü-mən\ *n, pl* **lumens** *also* **lu-mi-na** \-mə-nə\ [NL *lumin-, lumen*, fr. L, light, air shaft, opening] (1873) 1 : the cavity of a tubular organ (the ~ of a blood vessel) 2 : the bore of a tube (as of a hollow needle or catheter) 3 : a unit of luminous flux equal to the light emitted in a unit solid angle by a uniform point source of one candle intensity — **lu-mi-nal** *also* **lu-men-al** \-mə-nᵊl\ *adj*

lumin- *or* **lumini-** *comb form* [ME *lumin-*, fr. L *lumin-, lumen*] : light (*luminiferous*)

lu-mi-naire \ˌlü-mə-'nar, -'ner\ *n* [F, lamp, lighting] (1921) : a complete lighting unit

lu-mi-nance \'lü-mə-nən(t)s\ *n* (1880) 1 : the quality or state of being luminous 2 : the luminous intensity of a surface in a given direction per unit of projected area

Exhibit 3

E-FILED on 4/27/07

IN THE UNITED STATES DISTRICT COURT

FOR THE NORTHERN DISTRICT OF CALIFORNIA

SAN JOSE DIVISION

XOFT, INC.,

Plaintiff,

v.

CYTYC CORPORATION; and PROXIMA THERAPEUTICS, INC.,

Defendants.

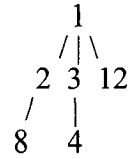
No. C-05-05312 RMW

CLAIM CONSTRUCTION ORDER

[Re Docket Nos. 48, 50, 53]

Xoft, Inc. sued Cytyc Corporation and one of its subsidiaries, Cytyc Surgical Products II, Inc., (collectively "Cytyc") for a declaratory judgment of non-infringement and invalidity of U.S. Patent Nos. 5,913,813 and 6,413,204. Cytyc responded by filing counterclaims for infringement of the same patents and currently asserts that Xoft infringes six claims of the '813 patent[1] and twenty

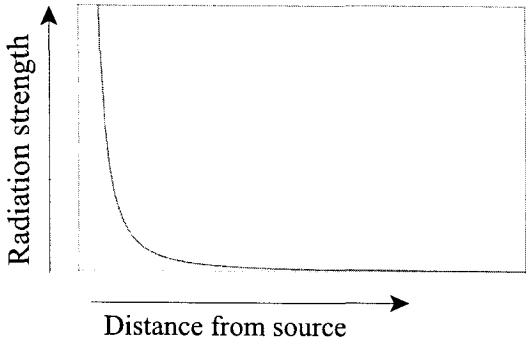
[1] Cytyc asserts claims 1, 2, 3, 4, 8, and 12. Claim 1 is an apparatus claim and the only independent claim of the '813 patent. Claims 2, 3, and 12 depend directly from claim 1. Claim 4 depends from claim 3, and claim 8 depends from claim 2. The following is a graphic representation of the relationship of the asserted claims:



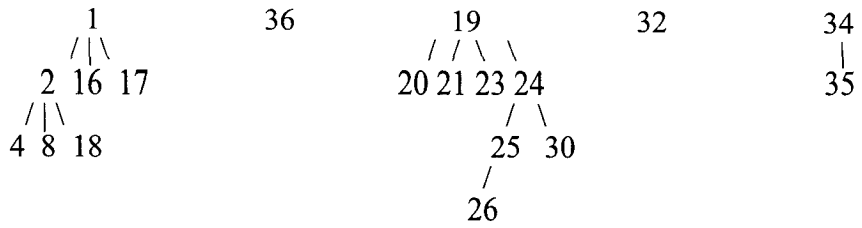
claims of the '204 patent[2]. The application for the '204 patent was filed as a continuation-in-part of the '813 patent; the former purports to incorporate by reference the latter. '204 patent, col. 1, ll. 10-11. The parties seek construction of eight terms or phrases from the '813 patent and twenty-one terms or phrases from the '204 patent.

I. BACKGROUND

The patents-in-suit are directed to methods and apparatus for treatment of proliferative tissue diseases. The prior art discloses that a radiation source can be implanted at a tumor site to irradiate any remaining diseased tissue; this process is known as interstitial brachytherapy. The parties agree that for the purposes of this suit, the strength of radiation may be assumed to decrease with the square of the distance from the radiation source. The graph of the equation $y = 1 / x^2$ thus can be used as an approximation of the relationship between the radiation strength and distance. The graph, shown below, illustrates that the radiation strength close to the radiation source is disproportionately higher than that at a relatively small distance away from the radiation source.

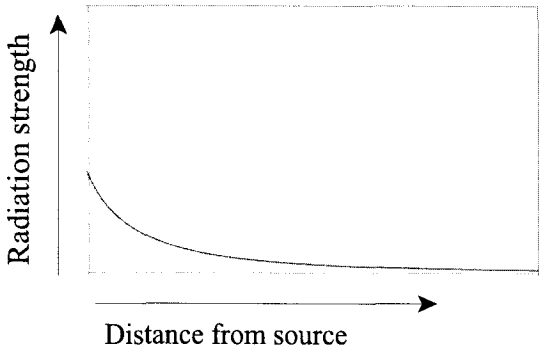


[2] Cytyc asserts claims 1, 2, 3, 4, 8, 16, 17, 18, 19, 20, 21, 23, 24, 25, 26, 30, 32, 34, 35, and 36 of the '204 patent. Claims 1 and 36 are the only independent apparatus claims. From claim 1 depend claims 2, 16, and 17. From claim 2 depend claims 4, 8, and 18. Claims 19, 32, and 34 are independent method claims. Claims 20, 21, 23, and 24 all depend from claim 19. Claim 25 depends from claim 24, and claim 26 depends from claim 25. Claim 30 also depends from claim 24. Claim 35 depends from claim 34. The following is a graphic representation of the relationship of the asserted claims:



This shows one of the problems encountered in radiation therapy, namely, that tissue close to the radiation source may get more radiation than a physician would prefer. When using interstitial therapy, a physician may wish to give all tissue within a certain distance—say, for example, 3 centimeters—from the tumor site a certain dose of radiation. However, tissue closer to the tumor site—say, 1 centimeter—will receive a much higher dose of radiation because of the inverse-square relationship. This means that healthy tissue near the tumor site may be killed by the radiation, which is an undesirable result.

Following the teachings of the patents-in-suit, the very high levels of radiation near the source can be avoided by simple mechanical means. Surrounding the radiation source on all sides with empty space (or some material other than living tissue) prevents the highest levels of radiation from affecting living tissue, giving the tissue a radiation dose profile that looks something like this:



II. ANALYSIS

A. Terms of the '813 patent

"Inner spatial volume"

Cytyc's proposed construction	*Xoft's proposed construction*
A region of space surrounded by an outer spatial volume that is defined by a closed inflatable chamber	Inner balloon in two-balloon device or spherical solid radionuclide in one-balloon device

The summary of the invention provides that

> it is possible to deliver a desired radiation dose at a predetermined radial distance from a source of radioactivity by providing a first spacial[3] volume at the distal end of a catheter and a second spacial volume defined by a surrounding of the first spatial

[3] Presumably all occurrences of "spacial" in the '813 patent should be read as "spatial."

> volume by a polymeric film wall where the distance from the spatial volume[4] and the wall is maintained substantially constant over their entire surfaces. One of the inner and outer volumes is filled with either a fluid or a solid containing a radionuclide(s) while the other of the two volumes is made to contain either a low radiation absorbing material, e.g., air or even a more absorptive material, such as an x-ray contrast fluid. Where the radioactive material comprises the core, the surrounding radiation absorbing material serves to control the radial profile of the radioactive emissions from the particular one of the inner and outer volumes containing the radionuclide(s) so as to provide a more radially uniform radiation dosage in a predetermined volume surrounding the outer chamber. Where the core contains the absorbent material, the radial depth of penetration of the radiation can be tailored by controlling the core size.

'813 patent, col. 1, l. 50-col. 2, l. 3. The first two claims of the '813 patent read:

> 1. Apparatus for delivering radioactive emissions to a body location with a uniform radiation profile, comprising:
>
> (a) a catheter body member having a proximal end and distal end;
>
> (b) an inner spatial volume disposed proximate the distal end of the catheter body member;
>
> (c) an outer, closed, inflatable, chamber defined by a radiation transparent wall affixed to the body member proximate the distal end thereof in surrounding relation to the inner spatial volume with a predetermined constant spacing between said inner spatial volume and the radiation transparent wall;
>
> (d) a material containing a radionuclide(s) disposed in one of the inner spatial volume and outer chamber; and
>
> (e) means disposed in the other of the inner spatial volume and outer chamber for rendering uniform the radial absorbed dose profile of the emissions from the one of the inner spatial volume and outer chamber containing the radionuclides.
>
> 2. The apparatus as in claim 1 wherein said inner spatial volume is an inner closed, chamber defined by a further radiation transparent wall.

'813 patent, col. 4, ll. 32-54. Since all claims of this patent other than claim 1 depend from claim 1, construction of "inner spatial volume" is critical.

In most embodiments of the invention disclosed in the patent specification, the inner spatial volume is a region of space surrrounded by an outer spatial volume that is defined by a closed inflatable chamber. *See* '813 patent, col. 2, ll. 44-63; col. 3, ll. 9-16, 42-48; col. 4, ll. 16-20; figs. 1,

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[4] Presumably this "spatial volume" should be taken to be the first spatial volume, which would mean that the polymeric film wall forms the outer boundary of the second spatial volume and that the second spatial volume is of a uniform thickness on all sides of the first spatial volume. Such a reading would comport with claim 1(c).

3-5. However, the patentee drafted the claims in such a way as to make clear that the inner spatial volume was not necessarily so limited:

> Those skilled in the art will appreciate that instead of having the inner spatial volume **30** defined by a generally spherical polymeric film wall as at **32**, the catheter body member **12** may have a solid spherical radiation emitting material in which event that solid sphere would be surrounded with the outer spherical wall **36** with the spatial volume therebetween occupied by a radioactive ray absorbent material, such as air, water or a contrast material.

'813 patent, col. 2, ll. 55-63.

Although somewhat awkwardly worded, the language of the patent allows for the inner volume to be defined by something other than a region enclosed by a polymeric wall. As Cytyc points out, Xoft's construction conflates the boundary of the volume with the volume itself. Cytyc's proposed construction, however, is a paraphrasing of the language of claim 1 that only clarifies a little the language of the patent. Furthermore, Cytyc's proposed construction would exclude an inner volume defined by a solid sphere, and thus cannot be correct.

Xoft objects that an abstract concept like a region of space cannot be part of an apparatus. Xoft is correct. However, the language of the patent does not imply that the inner volume is ever defined by something other than a physical object. In all embodiments of the invention disclosed in the '813 patent, the boundary of the inner volume is either a polymeric film wall or the edge of a solid sphere. Furthermore, it would seem difficult to fill one volume with radioactive liquid and the other with another fluid if the two volumes were not separated by some structure (which would necessarily be the outer boundary of the inner spatial volume.) *See* '813 patent, col. 1, ll. 57-62. The patent is even entitled "Double-Wall Balloon Catheter for Treatment of Proliferative Tissue." Xoft's expert, Dr. Lovoi, acknowledged that an "inner spatial volume" is a volume that is inside another volume. Lovoi Dep. at 101:25-102:7. The court defines "inner spatial volume" as "a region of space surrounded by an outer spatial volume and either enclosed by a polymeric film wall or defined by the edge of a solid radionuclide sphere."

Claim Language	*Court's Construction*
"inner spatial volume"	a region of space surrounded by an outer spatial volume and either enclosed by a polymeric film wall or defined by the outside surface of a solid radionuclide sphere

"Outer, closed, inflatable chamber"

Cytyc's proposed construction	*Xoft's proposed construction*
(no construction required)	Inflatable balloon, i.e., deflated balloon

Part (c) of claim 1 explains that the "outer, closed, inflatable chamber" is "defined by a radiation transparent wall affixed to the body member proximate the distal end thereof in surrounding relation to the inner spatial volume with a predetermined constant spacing between said inner spatial volume and the radiation transparent wall." '813 patent, col. 4, ll. 40-45. The preferred embodiment recites a similar structure: "Surrounding the spatial volume **30** is an outer chamber **34** defined by an outer polymeric film wall **36** that is appropriately spaced from the wall **32** of the inner chamber **30** when the two chambers are inflated or otherwise filled and supported." '813 patent, col. 2, ll. 37-41. There is no support in the patent for Xoft's argument that "outer, closed, inflatable chamber" should be limited to only a balloon in a deflated state. The court will therefore adopt Cytyc's proposal and not otherwise define this term.

Claim Language	*Court's Construction*
"outer, closed, inflatable chamber"	outer, closed, inflatable chamber

"Predetermined constant spacing"

Cytyc's proposed construction	*Xoft's proposed construction*
(no construction required)	(indefinite)

"Predetermined constant spacing between said inner spatial volume and radiation transparent wall"

Cytyc's proposed construction	*Xoft's proposed construction*
The spacing between the inner spatial volume and the radiation transparent wall of the outer, closed, inflatable chamber, when inflated, can be made constant in all directions if the outer chamber is spherical, or constant along a radial plane if the outer chamber is not spherical	(indefinite)

Xoft argues that the '813 patent is indefinite because it does not disclose how one "predetermines" the amount of spacing. Xoft points out that the spacing between the edges of the inner and outer volumes may change as parts of the apparatus are inflated or deflated, so the spacing is not constant. Cytyc's expert explained that "predetermined constant spacing" means that "the

spacing between the inner spatial volume and the wall of the outer inflatable chamber can be made constant in all directions if the outer chamber is spherical, or constant along a radial direction if non-spherical, whenever the outer chamber is inflated." Su Decl. (dkt. # 49), Ex. D (Verhey Decl.) at 7 (citations omitted). Cytyc also argues that "[o]ne skilled in the art knows how to determine an appropriate 'predetermined constant spacing' and Xoft provides no evidence, testimony, or case law to the contrary. Xoft cannot possibly show that the term is indefinite by clear and convincing evidence." Reply Br. (dkt. # 53) at 15.

Because 35 U.S.C. § 282 gives a patent "a statutory presumption of validity," a challenger bears the burden of proving "by clear and convincing evidence" that a patent is invalid. *Monsanto Co. v. Scruggs*, 459 F.3d 1328, 1336-37 (Fed. Cir. 2006). "[P]atent documents need not include subject matter that is known in the field of the invention." *S3 Inc. v. NVIDIA Corp.*, 259 F.3d 1364, 1371 (Fed. Cir. 2001). From the testimony of Dr. Verhey, it appears that one skilled in the art would know how to "predetermine" the amount of spacing.[5] *See* Tr. at 56-61, 85-89. Xoft offered no evidence suggesting otherwise. As the burden of proof is Xoft's, its indefiniteness argument necessarily fails given the absence of supporting evidence. The court will therefore adopt Cytyc's proposed construction of "predetermined constant spacing between said inner spatial volume and radiation transparent wall" modified only to make the definition easier to understand. A separate construction for "predetermined constant spacing" is not necessary.

Claim Language	*Court's Construction*
"predetermined constant spacing"	(no construction necessary)
"predetermined constant spacing between said inner spatial volume and radiation transparent wall"	spacing predetermined by one skilled in the art between the wall or edge of the inner spatial volume and the radiation transparent wall of the outer, closed, inflatable chamber, when inflated, which is constant in all directions if the outer chamber is spherical, or constant along a radial plane if the outer chamber is not spherical

[5] Xoft argues that the size of the cavity determines the size of the apparatus when fully inflated, but this alone does not determine the spacing between the inner spatial volume and the wall of the outer chamber.

"Rendering uniform"

Cytyc's proposed construction	*Xoft's proposed construction*
(no construction required)	Making the same, i.e., causing to have the same value or characteristic at all points.

"Means . . . for rendering uniform the radial absorbed dose profile of the emissions"

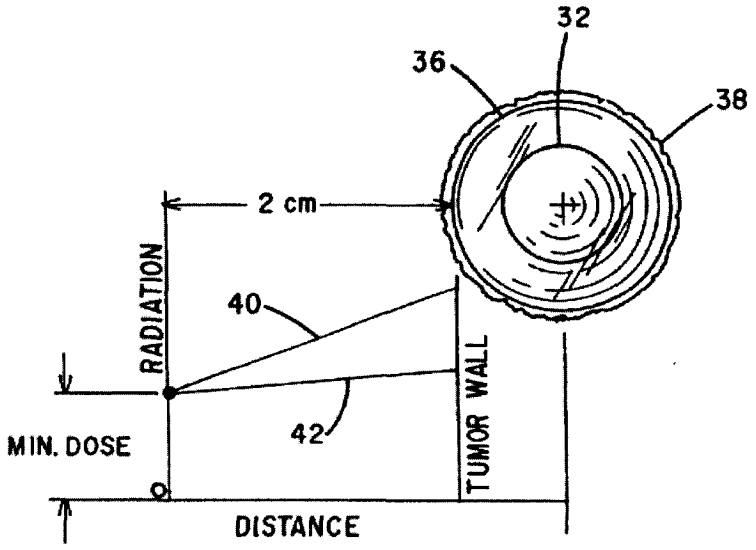
Cytyc's proposed construction	*Xoft's proposed construction*
Function: Modifying the ratio of the absorbed dose at a depth of interest in the target tissue to the absorbed dose at the surface of the tissue. Structure: A radiation absorbing or attenuating material, *e.g.*, air, x-ray contrast fluid, contrast media used in angiography, water, a gas, or barium sulfate.	Function: Making the dose along a radius extending from the radionuclide outwardly from the outer chamber wall the same at every point on the radius. Structure: No such means disclosed in '813 patent, means for making more uniform disclosed as substance within outer chamber.

Xoft's argument is that "uniform" must be taken literally, and the apparatus must produce radiation that does not decrease in strength with increasing distance from the source.[6] The parties do not dispute that Xoft's construction would require a physical impossibility; the strength of radiation necessarily decreases with distance from its source. Xoft, however, seeks to interpret "uniform" in a vacuum. The meaning of a particular word in a claim must be interpreted in light of the rest of the patent. *Ekchian v. Home Depot, Inc.*, 104 F.3d 1299, 1303 (Fed. Cir. 1997).

While the patent could have been drafted with more clarity, it is readily apparent that the patentee did not contemplate absolute uniformity. Figure 4 of the patent (reproduced below) is a comparison between the distance versus radiation dose plots of two scenarios. Line **40** shows the radiation dose that would result if chamber **36** were filled with a radioactive fluid. '813 patent, col. 3, ll. 20-24. Line **42** shows the radiation dose that would result if, following the teachings of the patent, the same radioactive fluid were contained only in chamber **32**. '813 patent, col. 3, ll. 24-28. As explained in the patent, "Comparing the plots **40** and **42**, by providing the concentric arrangement depicted, the absorbed dose profile in the space between the 2 cm site and the wall of the outer balloon is maintained much more uniform, thus preventing over-treatment of body tissue at

[6] Xoft also stated that it would "submit a Motion for Summary Judgment on this issue prior to the conduct of the *Markman* hearing," Responsive Br. (dkt. # 50) at 14, but did not do so.

or close to the outer wall **36** of the instrument." '813 patent, col. 3, ll. 28-33.



The patentee obviously did not expect absolute uniformity of radiation dosing. To interpret "uniform" in the manner urged by Xoft would go against the clear intent of the patentee. In *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443 (Fed. Cir. 1986), the defendant made a similar argument regarding the patentee's use of the term "smooth" with respect to the edges of contact lenses. The Federal Circuit looked to the intrinsic evidence and found that "smooth" did not mean absolutely ridge free but rather that it meant "smooth enough to serve the inventor's purposes, *i.e.*, not to inflame or irritate the eyelid of the wearer or be perceived by him at all when in place." *Id.* at 450. In this case, the inventor's purpose was to deliver radiation more uniformly than had previously been done, "thus preventing over-treatment of body tissue at or close to the outer wall . . . of the instrument." '813 patent, col. 3, ll. 28-32. The court will therefore define "rendering uniform" to mean to make the absorbed dose of radiation more uniform in order to prevent over-treatment of body tissue at or close to the outer wall of the instrument.

Since limitation language "means . . . for rendering uniform the radial absorbed dose profile of the emissions" is in means-plus-function format, the function must be construed and the corresponding structure or its equivalent identified in the specification. *BBA Nonwovens Simpsonville, Inc. v. Superior Nonwovens, L.C.C.*, 303 F.3d 1332, 1343 (Fed. Cir. 2002). As discussed, Xoft's definition of the function requires absolute uniformity which is not possible and which is not what the patent requires or the inventor intended. Cytyc's proposed definition construes the function as "modifying the ratio of the absorbed dose at a depth of interest in the target tissue to

the absorbed dose at the surface tissue." Although this appears to be a function of the invention, Cytyc's definition is too broad because it encompasses absorbed doses at the surface tissue that are not substantially uniform to absorbed doses at the target tissue. In other words, Cytyc's definition would not only encompass the radiation dose profile of line **42** above, but would also encompass the radiation doese profile of line 40. Furthermore, all radiation dose profiles between line 40 and line 42 that result in over-treatment of the surface tissue would also be included under Cytyc's definition. A more accurate construction of the function would require the absorbed dose at the target tissue and the absorbed dose at the surface tissue to be more uniform to prevent over-treatment of the surface tissue. Thus, the court defines the function of the "means . . . for rendering uniform the radial absorbed dose profile of the emissions" as making the absorbed dose of radiation more uniform to prevent over-treatment of body tissue at or close to the outer wall of the instrument.

Cytyc also identifies a radiation-absorbing or -attentuating material as the corresponding structure. At the claim construction hearing, Xoft argued that the uniformity of the radiation dose curve is solely affected by distance from the radiation source; the parties agree that this is true. *See* Tr. at 60-61. Although the composition of the material is not critical to the function, the radiation-absorbing or -attenuating material provides the distance necessary for achieving the uniformity in radiation dose curve. Thus, the court construes the language consistently with Cytyc's position.

Claim Language	*Court's Construction*
"rendering uniform"	to make the absorbed dose of radiation more uniform to prevent over-treatment of body tissue at or close to the outer wall of the instrument
"Means . . . for rendering uniform the radial absorbed dose profile of the emissions"	Function: Making the absorbed dose of radiation more uniform to prevent over-treatment of body tissue at or close to the outer wall of the instrument. Structure: A radiation absorbing or attenuating material, *e.g.*, air, x-ray contrast fluid, contrast media used in angiography, water, a gas, or barium sulfate or their equivalents.

"The radioactive material"

Cytyc's proposed construction	*Xoft's proposed construction*
The material of claim 1 containing a radionuclide.	(indefinite)

Claim 8 of the patent covers "[t]he apparatus as in claim 2 wherein the inner chamber contains the radioactive material." Claim 2 depends from claim 1. The parties dispute whether "a material containing a radionuclide(s)" suffices as an antecedent basis for "the radioactive material." It is readily apparent that the "radioactive material" in claim 8 refers back to "a material containing a radionuclide" described in claim 1, since "radionuclide" is the only radioactive material mentioned in claim 1. Anyone skilled in the art would so conclude. Xoft's contention that the term "radioactive material" is indefinite because it contains no antecedent basis is without merit. Xoft offers no authority suggesting that the antecedent basis of a term used in a dependent claim must be stated in identical words.[7] The court, therefore construes "the radioactive material" in claim 8 to be the "radionuclide(s)" referred to in claim 1.

Claim Language	*Court's Construction*
"The radioactive material"	The material of claim 1 containing a radionuclide.

"A plurality of radioactive solid particles placed at predetermined locations within the inner spatial volume to provide a desired composite radiation profile"

Cytyc's proposed construction	*Xoft's proposed construction*
A plurality of radioactive solid particles placed at pre-determined locations within the inner spatial volume to provide a desired dose profile that is the sum of the radiation profiles of the plurality of particles.	Static array of solid radioactive particles each placed in a single location and mounted on distal ends of separate wires. Desired composite radiation profile" is indefinite.

Claim 12 of the patent is directed to "[t]he apparatus as in claim 1 wherein the material containing a radionuclide comprises a plurality of radioactive solid particles placed at predetermined locations within the inner spatial volume to provide a desired composite radiation profile." Xoft argues claim 12 is indefinite on two grounds: first, that "desired composite radiation profile" is not

[7] At the *Markman* hearing, Xoft stated that it would provide a citation to such supporting authority. Tr. at 64. Xoft, however, has not done so.

defined, and second, that "inner spatial volume" is indefinite because no physical structure bounds it. The court rejects Xoft's second argument for the reasons given when construing "inner spatial volume" above. The court rejects Xoft's first argument because it presents no evidence that one skilled in the art would not understand "desired composite radiation profile."[8] Cytyc's proposed construction does not clarify the meaning of claim 12. However, since the language is understandable as is, no construction of "a plurality of radioactive solid particles placed at predetermined locations within the inner spatial volume to provide a desired composite radiation profile" is necessary or appropriate.

Claim Language	*Court's Construction*
"A plurality of radioactive solid particles placed at predetermined locations within the inner spatial volume to provide a desired composite radiation profile"	(no construction needed)

B. Terms of the '204 patent

Claim 1 of the '204 patent is similar to claim 1 of the '813 patent. Claim 1 of the '204 patent describes:

> An interstitial brachytherapy apparatus for delivering radioactive emissions to an internal body location comprising:
>
> (a) a catheter body member having a proximal end and distal end;
>
> (b) an inner spatial volume disposed proximate to the distal end of the catheter body member;
>
> (c) an outer spatial volume defined by an expandable surface element disposed proximate to the distal end of the body member in a surrounding relation to the inner spatial volume; and
>
> (d) a radiation source disposed in the inner spatial volume and generating a three-dimensional isodose profile that is substantially similar in shape to the expandable surface element.

[8] It would seem that for one skilled in the art, it would be a relatively simple matter to add up the individual radiation profiles of individual particles. *See* Tr. at 75-76.

"Interstitial"

Cytyc's proposed construction	*Xoft's proposed construction*
(no construction required)	Site in natural or surgically created cavity in body.

"Brachytherapy"

Cytyc's proposed construction	*Xoft's proposed construction*
Radiation therapy delivered by a spatially confined radiation source at or near the site of the diseased tissue.	Radiation therapy delivered by a spatially confined radionuclide at or near a tumor or other proliferative tissue disease site.

"Interstitial brachytherapy"

Cytyc's proposed construction	*Xoft's proposed construction*
Brachytherapy applied directly to the interspaces of a body tissue, where the interspaces are not naturally occurring.	Radiation therapy delivered by a spatially confined radionuclide at or near a tumor site in a natural or surgically created cavity in a body.

Cytyc argues that "interstitial" and "brachytherapy" should be constructed together; Xoft seeks a separate construction for each word. Cytyc also complains that Xoft seeks to limit "brachytherapy" to radionuclides, arguing that the definition should encompass any radiation source. However, the patent provides a clear definition of "brachytherapy": "The term 'brachytherapy,' as used herein, refers to radiation therapy delivered by a spatially confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site." '204 patent, col. 1, ll. 30-33. Here, the patentee clearly acted as his own lexicographer, and Cytyc's arguments for a broader definition do not acknowledge this clear definition. The court construes "brachytherapy" to mean "radiation therapy delivered by a spatially-confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site."[9]

Xoft argues that "interstitial" means any body cavity, while Cytyc argues that "interstitial" should be limited to only non-naturally-occurring cavities. As Xoft points out, one medical dictionary defines "interstitial" as "1. Placed or lying between. 2. Pert. to

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[9] This definition does not resolve the parties' dispute over whether "radioactive material" should be read to encompass only "radionuclides" (as Xoft wishes) or any "radiation source" (as Cytyc urges). As the parties have separately sought construction of "radioactive material," the court will address construction of that phrase below.

interstices or spaces within an organ or tissue." TABER'S CYCLOPEDIC MEDICAL DICTIONARY, 1007 (Clayton M. Thomas, ed., 17th ed. 1993). Although not cited by the parties, a British oncology text indicates that "interstitial" has a particular meaning in the field of the invention:

> Two main techniques are used for the delivery of radiation which is given either as an external beam or as short range radiation from an implanted radioactive source. External beam radiation usually involves megavoltage produced by linear accelerator as photons or electrons or from cobalt sources in the form of relative low energy X-rays or gamma rays. The latter are often used to treat relatively superficial lesions such as basal cell carcinoma or recurrences within the skin. High energy radiation can be used to treat deeply located lesions such as prostatic carcinomas without delivering an excessive dose to adjacent normal tissue. . . .
>
> Interstitial implant irradiation gives a high local dose to the tumour and usually employes sources such as radium, iridium, or caesium used in the form of needles or wires implanted in the tumour. This technique is widely used in the treatment of head and neck cancers to deliver a high tumour dose without irradiation to sensitive organs such as the lens of the eye or the spinal cord.

I.S. Fentiman, *The local Treatment of Cancer*, INTRODUCTION TO THE CELLULAR & MOLECULAR BIOLOGY OF CANCER, 434, 446 (L.M. Franks & N.M. Teich, eds., 2d ed. 1991).

However, Cytyc points out that regardless of any generally-accepted meaning of "interstitial" in the field of the invention, the patentee limited "interstitial" during prosecution to refer to only surgically-created cavities (and similarly defined "intercavital" to refer to natural body cavities):

> Turning to the cited prior art, the Ishiwara device comprises a thermotherapeutic apparatus having a catheter body member, an inner lumen surrounded by an outer lumen, and a radiation source contained within the inner lumen. . . . Ishiwara's apparatus is inserted into a body cavity. Hence, the apparatus does not provide *interstitial* radiation treatment, as Applicant's invention requires, but rather intercavital radiation treatment.

Su Decl. (dkt. # 49), Ex. C (Amendment & Resp.) at 11 (citations omitted). This is consistent with the background section of the patent, which mentions surgical cavities several times but not natural ones. '204 patent, col. 1, ll. 19, 23, 25, 63, col. 2, l. 1. Also, although the summary section does not specify what type of cavities the apparatus claims are directed to, the summary makes clear that the method claims are directed to a method that "includes surgically creating access to the proliferating tissue within a patient and surgically resecting at least a portion of the proliferating tissue to create a resection cavity within body tissue." *Id.*, col. 3, ll. 3-6.

The parties did not brief the issue of how much weight the court should afford the prosecution history in this instance.[10] The Federal Circuit has instructed that "[a]lthough prosecution history can be a useful tool for interpreting claim terms, it cannot be used to limit the scope of a claim unless the applicant took a position before the PTO that would lead a competitor to believe that the applicant had disavowed coverage of the relevant subject matter." *Schwing GmbH v. Putzmeister Aktiengesellschaft*, 305 F.3d 1318, 1324 (Fed. Cir. 2002). Here, the patentee clearly disavowed coverage of intercavitary radiation treatment when arguing to the PTO. Given the

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[10] In its recent *en banc* explanation of the evidence to be used in construing claims, the Federal Circuit devoted a paragraph to prosecution history:

> In addition to consulting the specification, we have held that a court "should also consider the patent's prosecution history, if it is in evidence." *Markman*, 52 F.3d at 980; *see also Graham v. John Deere Co.*, 383 U.S. 1, 33, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966) ("[A]n invention is construed not only in the light of the claims, but also with reference to the file wrapper or prosecution history in the Patent Office."). The prosecution history, which we have designated as part of the "intrinsic evidence," consists of the complete record of the proceedings before the PTO and includes the prior art cited during the examination of the patent. *Autogiro*, 384 F.2d at 399. Like the specification, the prosecution history provides evidence of how the PTO and the inventor understood the patent. *See Lemelson v. Gen. Mills, Inc.*, 968 F.2d 1202, 1206 (Fed. Cir. 1992). Furthermore, like the specification, the prosecution history was created by the patentee in attempting to explain and obtain the patent. Yet because the prosecution history represents an ongoing negotiation between the PTO and the applicant, rather than the final product of that negotiation, it often lacks the clarity of the specification and thus is less useful for claim construction purposes. *See Inverness Med. Switz. GmbH v. Warner Lambert Co.*, 309 F.3d 1373, 1380-82 (Fed. Cir. 2002) (the ambiguity of the prosecution history made it less relevant to claim construction); *Athletic Alternatives, Inc. v. Prince Mfg., Inc.*, 73 F.3d 1573, 1580 (Fed. Cir. 1996) (the ambiguity of the prosecution history made it "unhelpful as an interpretive resource" for claim construction). Nonetheless, the prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be. *Vitronics*, 90 F.3d at 1582-83; *see also Chimie v. PPG Indus., Inc.*, 402 F.3d 1371, 1384 (Fed. Cir. 2005) ("The purpose of consulting the prosecution history in construing a claim is to 'exclude any interpretation that was disclaimed during prosecution.'"), quoting *ZMI Corp. v. Cardiac Resuscitator Corp.*, 844 F.2d 1576, 1580 (Fed. Cir. 1988); *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1576 (Fed. Cir. 1995).

Phillips v. AWH Corp., 415 F.3d 1303, 1317 (Fed. Cir. 2005) (*en banc*).

intrinsic evidence is of primary importance[11] and all supports Cytyc's position, the court construes "interstitial" to mean "involving a surgically-created cavity in a body."

In light of the constructions of "interstitial" and "brachytherapy" above, no further construction of "interstitial brachytherapy" is necessary.

Claim Language	*Court's Construction*
"interstitial"	involving a surgically-created cavity in a body
"brachytherapy"	radiation therapy delivered by a spatially-confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site
"interstitial brachytherapy"	(no construction necessary)

"Inner spatial volume"

Cytyc's proposed construction	*Xoft's proposed construction*
A region of space surrounded by an outer spatial volume that is defined by an expandable surface element	Inner balloon in two-balloon device or spherical solid radionuclide in one-balloon device.

The phrase "inner spatial volume" appears in both patents-in-suit. The parties' arguments regarding the meaning of "inner spatial volume" are similar for each patent. The relevant portions of the specification are the same, and, additionally, the '204 patent purports to incorporate by reference the '813 patent. '204 patent, col. 1, ll. 10-11. The court will therefore construe "inner spatial volume" in the '204 patent in the same manner as for the '813 patent.

Claim Language	*Court's Construction*
"inner spatial volume"	a region of space surrounded by an outer spatial volume and either enclosed by a polymeric film wall or defined by the outside surface of a solid radionuclide sphere.

[11] The extrinsic evidence that Cytyc used "intercavitary" in literature and advertising in a manner that encompasses the definitions of "interstitial" and "intercavitary" it advances now, *see* Tr. at 93, is of little weight in this situation. Similarly, evidence presented by Cytyc that Xoft represented to the FDA that the term "interstitial" "is a more appropriate word for a cavity that is surgically created as compared to a natural body cavity," (*see* Decl. of Henry Su Supp. Cytyc's Scupplemental Claim Construction Br., Ex. A, is not entitled to significant weight although it does suggest that one skilled in the art construes the term as Cytyc proposes.

"Outer spatial volume"

Cytyc's proposed construction	*Xoft's proposed construction*
(no construction required) *or* A region of space defined by an expandable surface element and surrounding an inner spatial volume.	Balloon or cage.

The phrase "outer spatial volume" in the '204 patent is analogous to the "outer, closed, inflatable chamber" of the '813 patent. The "outer spatial volume" is also explained in a similar manner; it is "defined by an expandable surface element disposed proximate to the distal end of the body member in a surrounding relation to the inner spatial volume." '204 patent, col. 8, ll. 22-25. Xoft again confuses the concepts of a volume with the boundary of a volume. Cytyc's proposed construction is congruent with the language of claim 1 of the '204 patent, so the court will construe "outer spatial volume" as "a region of space defined by an expandable surface element and surrounding an inner spatial volume."

Claim Language	*Court's Construction*
"outer spatial volume"	a region of space defined by an expandable surface element and surrounding an inner spatial volume

"Expandable surface element"

Cytyc's proposed construction	*Xoft's proposed construction*
(no construction required) *or* A device that can be expanded or inflated, such as an expandable cage or an inflatable balloon.	Deflated balloon or collapsed cage.

Xoft's basic argument is that "expandable surface element" must be a deflated structure because once something is fully inflated, it is no longer expandable. Xoft also points out that part (d) of claim 1 refers to the "isodose profile" being "substantially similar in shape to the expandable surface element" without specifying whether the expandable surface element is fully expanded. It is apparent that the patentee intended "expandable surface element" to refer to a structure whether it was fully inflated or not. Xoft's proposed construction would have this element wink out of

existence at full inflation, leaving the "outer spatial volume" unbounded and giving the "isodose profile" no shape. The court agrees with Cytyc that no construction of the term is necessary.

Claim Language	*Court's Construction*
"expandable surface element"	(no construction needed)

"Radiation source"

Cytyc's proposed construction	*Xoft's proposed construction*
(no construction required)	radionuclide

The patent provides a clear definition of "brachytherapy": "The term 'brachytherapy,' as used herein, refers to radiation therapy delivered by a spatially confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site." All asserted independent claims of the '204 patent contain the phrase "interstitial brachytherapy," which the court has construed as "radiation therapy delivered by a spatially-confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site." Cytyc's argument that "radiation source" should not be constructed to exclude any radiation sources must be rejected; the claims clearly do not contemplate a radiation source other than "radioactive material."

There is still, however, the question of whether "radioactive material" means the same thing as Xoft's proposed construction of "radionuclide."[12] In describing the preferred embodiment, the patent says: "[t]he inner volume **30** is then filled with a material containing a predetermined radionuclide, for example, I-125, I-131, Yb-169 *or other source of radiation, such as radionuclides that emit photons, beta particles, gamma radiation, or other therapeutic rays.*" '204 patent, col. 4, ll. 9-13 (emphasis added). Since all the examples of sources of radiation given in the specification are radionuclides, the patentee appears to have intended to define "radioactive material" as "radionuclides." Cytyc argued at the *Markman* hearing that "or other therapeutic rays" could refer to other sources such as x-rays. The words "or other therapeutic rays," however, clearly refers to types

[12] The parties have agreed that "radionuclide" means "an isotope that undergoes radioactive decay."

of radionuclides. Cytyc's construction would require the patentee to have inserted the word "or" before "gamma radiation," indicating the end of the list of types of radionuclides.[13]

Dictionary definitions are consistent with construing "radiation source" as a "radionuclide." One definition of "radioactive" is "[a] descriptive term for a material made up of atoms in which radioactivity occurs." AMERICAN HERITAGE NEW DICTIONARY OF CULTURAL LITERACY (3d ed. 2006). A medical dictionary provided by Xoft defines "radioactive" as "giving off radiation as the result of the disintegration of the nucleus of an atom." MOSBY'S MEDICAL, NURSING, AND ALLIED HEALTH DICTIONARY, 1326 (Kenneth N. Anderson *et al.* eds., 4th ed. 1994). Cytyc has not presented evidence that one skilled in this art would understand "radioactive material" any differently. The court agrees with Xoft—the term "radioactive" in the context of the '204 patent does not encompass such radiation sources as x-ray tubes, and "radiation source" therefore should be taken to mean "radionuclide."

Claim Language	*Court's Construction*
"radiation source"	radionuclide

"Minimum prescribed dose"

Cytyc's proposed construction	*Xoft's proposed construction*
Minimum prescribed dose received within a target tissue for delivering therapeutic effects.	Minimum dose needed to treat cancer cells.

The parties have requested construction of the phrase "minimum prescribed dose" and point out that the term appears in claims 2, 18, 24, 32, and 36 of the '204 patent. The parties do not argue that the term should be construed differently for different claims. However, claims 2, 24, 32, and 36 contain the phrase "minimum prescribed absorbed dose," and claim 18 contains the phrase "prescribed absorbed dose." These inconsistencies seem irrelevant, however, because the parties'

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[13] Cytyc also stated that this was an "Oxford comma" issue. Tr. at 137-38. However, in the sentence at issue, the Oxford comma is the one after "gamma radiation." Whether it is present does not alter the meaning of the sentence. Cytyc also argued that "we're in the land of eats, shoots and leaves." If Cytyc was referring to a book of such title, the court does not see how that would support Cytyc's argument; the theme of *Eats, Shoots & Leaves* is that punctuation should be used correctly. *See* Lynne Truss, *Eats, Shoots & Leaves: The Zero Tolerance Approach to Punctuation* (2004).

dispute is whether any such doses should be limited to treatment of cancer cells or allowed to cover any potential therapeutic effects. The court's construction of "brachytherapy" limits the claims to treatments "at or near a tumor or other proliferative tissue disease site." Xoft's proposed construction is too narrow, and Cytyc's is too broad. However, in light of the construction of "brachytherapy," no construction of "minimum prescribed dose" or similar phrases is necessary.

Claim Language	*Court's Construction*
"minimum prescribed dose"	(no construction necessary)

"Delivering a prescribed absorbed dose"

Cytyc's proposed construction	*Xoft's proposed construction*
(no construction required)	(indefinite)

Xoft argues that the patent does not reveal how one goes about prescribing a dose using the device, and that the phrase "delivering a prescribed absorbed dose" is therefore fatally indefinite. The '204 patent, however, describes a tool for treating proliferative tissue disease. A patent could adequately describe and claim a new apparatus or method for making the corrective curves in contact lenses, but a description of the particular curves a patient might require would not be necessary. If those skilled in the art would know how to use the disclosed invention, describing how to use it is unnecessary—the patentee merely needs to adequately describe the invention. Since Xoft bears the burden of proving that those skilled in the art would not know how to use the tool or method described in the patent and has presented no evidence on the subject, the court rejects Xoft's contention that the phrase is indefinite. No construction is necessary.

Claim Language	*Court's Construction*
"delivering a prescribed absorbed dose"	(no construction necessary)

"The inner and outer spatial volumes are configured to provide a minimum prescribed absorbed dose"

Cytyc's proposed construction	*Xoft's proposed construction*
The inner and outer spatial volumes are configured to provide a minimum prescribed absorbed dose for delivering	(indefinite)

"The inner and outer spatial volumes are configured to provide a minimum prescribed absorbed dose"

Cytyc's proposed construction	*Xoft's proposed construction*
Configuring the inner and outer spatial volumes to provide a minimum prescribed absorbed dose for delivering therapeutic effects to a target tissue.	(indefinite)

The phrases "the inner and outer spatial volumes are configured to provide a minimum prescribed absorbed dose" and "configuring the inner and outer spatial volumes to provide a minimum prescribed absorbed dose" are not indefinite for essentially the same reasons given in the previous section. As Cytyc again appears to be attempting to impermissibly broaden its claims to capture any therapeutic effect, despite the clear limitation provided by the patentee's definition of "brachytherapy," the court also cannot adopt Cytyc's proposed construction. No construction of the disputed language is necessary in light of the court's construction of other terms in the patent.

Claim Language	*Court's Construction*
"the inner and outer spatial volumes are configured to provide a minimum prescribed absorbed dose"	(no construction necessary)
"the inner and outer spatial volumes are configured to provide a minimum prescribed absorbed dose"	(no construction necessary)

"A minimum distance outward from the outer spatial volume expandable surface"

Cytyc's proposed construction	*Xoft's proposed construction*
(no construction required)	(indefinite)

Claims 2, 24, 32, and 36 all include the phrase "the target tissue being defined between the outer spatial volume expandable surface and a minimum distance outward from the outer spatial volume expandable surface."[14] Xoft asserts that "minimum distance" is indefinite in this context because the patent does not explain how the minimum distance is determined.

[14] The court believes that one skilled in the art would understand that the patentee intended to define "target tissue" as the tissue "between the outer spatial volume expandable surface and a minimum distance outward from the outer spatial volume expandable surface." Taken literally, the patent explains the physical location where the act of defining "target tissue" takes place.

Here, "minimum" does not appear to add anything to the patent. The "target tissue" is the tissue outside of the outer chamber for a fixed distance in all directions, but this fixed distance or how one determines it are not explained. It seems that one skilled in the art would know how to determine the distance. *See* Tr. at 85-89. But the patent may as well read "a short distance outward" or "a determined distance outward" or merely "a distance outward."

Cytyc claims that specification provides some guidance and that the minimum distance may in some instances be between half and one centimeter. The specification does state that

> device A can readily be configured to provide a dose in a therapeutic range, say between 40 to 60 Gray, at a distance between 0.5 and 1.0 cm from the outer spatial volume for an outer spatial volume having a diameter of 4.0 cm and being in contact with the resection cavity wall.

'204 patent, col. 6, ll. 31-35. However, Cytyc neglects to mention that "device A" is "an interstitial brachytherapy apparatus . . . such as those employed in U.S. Pat. No. 5,429,582, having a single spatial volume **50** filled with a radioactive material in solution." '204 patent, col. 6, ll. 3-7. In any case, this discussion does not use the phrases "target tissue" or "a minimum distance outward." Nevertheless, Xoft has presented no evidence that one skilled in the art would not understand the phrase "the target tissue being defined between the outer spatial volume expandable surface and a minimum distance outward from the outer spatial volume expandable surface." Xoft has not met its burden of proving by clear and convincing evidence that this language is indefinite, and the court finds that no construction is necessary.

Claim Language	*Court's Construction*
"a minimum distance outward from the outer spatial volume expandable surface"	(no construction necessary)

"Controlled dose"

Cytyc's proposed construction	*Xoft's proposed construction*
(no construction required)	(indefinite)

"To reduce or prevent necrosis in healthy tissue proximate to the expandable surface"

Cytyc's proposed construction	*Xoft's proposed construction*
(no construction required)	(indefinite)

"Providing a controlled dose at the outer spatial volume expandable surface to reduce or prevent necrosis in healthy tissue"

Cytyc's proposed construction	*Xoft's proposed construction*
Controlling the ratio of the dose at the expandable surface of the outer spatial volume to the prescribed dose at the depth of interest in the target issue so that the dose at the expandable surface is not so high that it lethally damages cells in healthy tissue in contact with the expandable surface	(indefinite)

Xoft argues that the patent does not reveal how one goes about controlling a dose using the device and that "reducing necrosis" is a hopelessly vague concept, making the '204 patent indefinite. Xoft, however, has presented no evidence that one skilled in the art would not be able to understand the patent and has again failed to meet its burden of proof. The court will therefore adopt Cytyc's construction proposals. "Providing a controlled dose at the outer spatial volume expandable surface to reduce or prevent necrosis in healthy tissue" means "controlling the ratio of the dose at the expandable surface of the outer spatial volume to the prescribed dose at the depth of interest in the target issue so that the dose at the expandable surface is not so high that it lethally damages cells in healthy tissue in contact with the expandable surface."

Claim Language	***Court's Construction***
"controlled dose"	(no separate construction necessary)
"to reduce or prevent necrosis in healthy tissue proximate to the expandable surface"	(no separate construction necessary)
"providing a controlled dose at the outer spatial volume expandable surface to reduce or prevent necrosis in healthy tissue"	controlling the ratio of the dose at the expandable surface of the outer spatial volume to the prescribed dose at the depth of interest in the target issue so that the dose at the expandable surface is not so high that it lethally damages cells in healthy tissue in contact with the expandable surface

"Adapting the expandable surface to contact tissue surrounding the resection cavity to conform the tissue"

Cytyc's proposed construction	*Xoft's proposed construction*
(no construction required)	(indefinite)

Xoft's contention that this phrase is indefinite springs from its argument that "expandable surface element" means "deflated balloon or cage." As the court has rejected Xoft's interpretation of "expandable surface element," no construction of "adapting the expandable surface to contact tissue surrounding the resection cavity to conform the tissue" is necessary.

Claim Language	*Court's Construction*
"adapting the expandable surface to contact tissue surrounding the resection cavity to conform the tissue"	(no construction necessary)

"Desired shape of the expandable surface element"

Cytyc's proposed construction	*Xoft's proposed construction*
(no construction required)	(indefinite)

Xoft has again presented no evidence to back up an argument that the phrase is indefinite and therefore again fails to carry its burden of proof. No construction of "desired shape of the expandable surface element" is necessary.

Claim Language	*Court's Construction*
"desired shape of the expandable surface element"	(no construction necessary)

"Predetermined spacing"

Cytyc's proposed construction	*Xoft's proposed construction*
(no construction required)	(indefinite)

"A predetermined spacing is provided between said inner spatial volume and the expandable surface element" / "A predetermined spacing between said inner spatial volume and the expandable surface element"

Cytyc's proposed construction	*Xoft's proposed construction*
The distance between the inner spatial volume and the expandable surface element is determined in advance	(indefinite)

Xoft's contention that these phrases are indefinite is based on its argument that "expandable surface element" means "deflated balloon or cage," and Xoft has again presented no evidence to back up arguments that the phrases are indefinite. No construction of "predetermined spacing" is necessary. The court will adopt Cytyc's proposals and define both of the long phrases ("a predetermined spacing is provided between said inner spatial volume and the expandable surface element" and "a predetermined spacing between said inner spatial volume and the expandable surface element") as "the distance between the inner spatial volume and the expandable surface element is determined in advance."

Claim Language	*Court's Construction*
"predetermined spacing"	(no construction necessary)
"a predetermined spacing is provided between said inner spatial volume and the expandable surface element" / "a predetermined spacing between said inner spatial volume and the expandable surface element"	the distance between the inner spatial volume and the expandable surface element is determined in advance

"Intraoperatively"

Cytyc's proposed construction	*Xoft's proposed construction*
(no construction required) *or* During the surgical operation to remove proliferative tissue.	After surgical removal of tumor but prior to closing the surgical site

At the claim construction hearing, the parties appeared to agree on the definition of "interoperatively." *See* Tr. at 140. The previous apparent disagreement revolved around whether the surgical site could be closed before insertion of the catheter apparatus. The court understands that the parties agree that the catheter must be inserted before the surgical site is closed. The '204 patent at column 7, lines 55-64, specifically refers to the catheter being inserted "[f]ollowing tumor resection, but prior to closing the surgical site."

Claim Language	*Court's Construction*
"intraoperatively"	following tumor resection, but prior to closing the surgical site

"Solid radiation source"

Cytyc's proposed construction	*Xoft's proposed construction*
A radiation source that has a fixed shape and volume, and is not deformable	Solid radionuclide

The parties' primary dispute here is whether "radiation source" encompasses more than radionuclides, which the court addressed above to limit "radiation source" to radionuclides. Cytyc presents a dictionary definition of "solid," namely, "of definite shape and volume; not liquid or gaseous," from the AMERICAN HERITAGE COLLEGE DICTIONARY, 1295 (3d ed. 1997). The court will therefore define "solid radiation source" as "a radionuclide of definite shape and volume; not liquid or gaseous."

Claim Language	*Court's Construction*
"solid radiation source"	a radionuclide of definite shape and volume; not liquid or gaseous

"The prescribed absorbed dose is delivered to the target tissue in substantially three dimensions"

Cytyc's proposed construction	*Xoft's proposed construction*
The prescribed absorbed dose is delivered to the target tissue such that all points at a given outward distance from the tissue wall will receive the same dose.	(indefinite)

Xoft contends that "prescribed absorbed dose" and "in substantially three dimensions" render "the prescribed absorbed dose is delivered to the target tissue in substantially three dimensions" fatally indefinite. The court has already rejected Xoft's argument regarding "prescribed absorbed dose."

Xoft points to Cytyc's expert's testimony that "there's no such thing as substantially three dimensions" because something is either three dimensional or not. Mulville Decl. (dkt. # 51), Ex. L (Verhey Decl.) at 153. Cytyc points to Xoft's expert's testimony that he could envision a brachytherapy apparatus that delivered 99 percent of its radiation in a plane; Cytyc claims such a flat radiation field would not be in substantially three dimensions. Though a closer question than some of Xoft's other indefiniteness contentions, the court nonetheless finds that Xoft has not shown by clear and convincing evidence that one skilled in the art would not understand "in substantially three

dimensions" in the manner put forth by Cytyc. The court therefore adopts Cytyc's proposed construction for "the prescribed absorbed dose is delivered to the target tissue in substantially three dimensions," namely, "the prescribed absorbed dose is delivered to the target tissue such that all points at a given outward distance from the tissue wall will receive the same dose."

Claim Language	*Court's Construction*
"the prescribed absorbed dose is delivered to the target tissue in substantially three dimensions"	the prescribed absorbed dose is delivered to the target tissue such that all points at a given outward distance from the tissue wall will receive the same dose

III. ORDER

1. For the reasons given above, the court adopts the following claim construction as detailed in this order.

Term or phrase	Court's construction
"inner spatial volume"	a region of space surrounded by an outer spatial volume and either enclosed by a polymeric film wall or defined by the outside surface of a solid radionuclide sphere.
"outer, closed, inflatable chamber"	outer, closed, inflatable chamber
"predetermined constant spacing"	(no construction necessary)
"predetermined constant spacing between said inner spatial volume and radiation transparent wall"	spacing predetermined by one skilled in the art between the wall or edge of the inner spatial volume and the radiation transparent wall of the outer, closed, inflatable chamber, when inflated, which is constant in all directions if the outer chamber is spherical, or constant along a radial plane if the outer chamber is not spherical
"rendering uniform"	to make the absorbed dose of radiation more uniform to prevent over-treatment of body tissue at or close to the outer wall of the instrument
"Means . . . for rendering uniform the radial absorbed dose profile of the emissions"	Function: Making the absorbed dose of radiation more uniform to prevent over-treatment of body tissue at or close to the outer wall of the instrument. Structure: A radiation absorbing or attenuating material, *e.g.*, air, x-ray contrast fluid, contrast media used in angiography, water, a gas, or barium sulfate or their equivalents.
"The radioactive material"	The material of claim 1 containing a radionuclide.
"A plurality of radioactive solid particles placed at predetermined locations within the inner spatial volume to provide a desired composite radiation profile"	(no construction needed)
"interstitial"	involving a surgically-created cavity in a body
"brachytherapy"	radiation therapy delivered by a spatially-confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site
"interstitial brachytherapy"	(no construction necessary)

"outer spatial volume"	a region of space defined by an expandable surface element and surrounding an inner "expandable surface element"(no construction needed)
"radiation source"	radionuclide
"minimum prescribed dose"	(no construction necessary)
"delivering a prescribed absorbed dose"	(no construction necessary)
"the inner and outer spatial volumes are configured to provide a minimum prescribed absorbed dose"	(no construction necessary)
"the inner and outer spatial volumes are configured to provide a minimum prescribed absorbed dose"	(no construction necessary)
"a minimum distance outward from the outer spatial volume expandable surface"	(no construction necessary)
"controlled dose"	(no separate construction necessary)
"to reduce or prevent necrosis in healthy tissue proximate to the expandable surface"	(no separate construction necessary)
"providing a controlled dose at the outer spatial volume expandable surface to reduce or prevent necrosis in healthy tissue"	controlling the ratio of the dose at the expandable surface of the outer spatial volume to the prescribed dose at the depth of interest in the target issue so that the dose at the expandable surface is not so high that it lethally damages cells in healthy tissue in contact with the expandable surface
"adapting the expandable surface to contact tissue surrounding the resection cavity to conform the tissue"	(no construction necessary)
"desired shape of the expandable surface element"	(no construction necessary)
"predetermined spacing"	(no construction necessary)
"a predetermined spacing is provided between said inner spatial volume and the expandable surface element" / "a predetermined spacing between said inner spatial volume and the expandable surface element"	the distance between the inner spatial volume and the expandable surface element is determined in advance
"intraoperatively"	following tumor resection, but prior to closing the surgical site
"solid radiation source"	a radionuclide of definite shape and volume; not liquid or gaseous

"the prescribed absorbed dose is delivered to the target tissue in substantially three dimensions"	the prescribed absorbed dose is delivered to the target tissue such that all points at a given outward distance from the tissue wall will receive the same dose

2. The parties shall appear for a further case management conference on June 1, 2007 at 10:30 a.m. and shall file a further joint case management conference statement no later than four days prior.

DATED: 4/27/07

Ronald M Whyte

RONALD M. WHYTE
United States District Judge

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Dated: 4/27/07

SPT
Chambers of Judge Whyte

Exhibit 4

US006413204B1

(12) **United States Patent**
Winkler et al.

(10) **Patent No.: US 6,413,204 B1**
(45) **Date of Patent: *Jul. 2, 2002**

(54) **INTERSTITIAL BRACHYTHERAPY APPARATUS AND METHOD FOR TREATMENT OF PROLIFERATIVE TISSUE DISEASES**

(75) Inventors: **Rance A. Winkler**, Atlanta; **Timothy J. Patrick**; **James Stubbs**, both of Alpharetta, all of GA (US)

(73) Assignee: **Proxima Therapeutics, Inc.**, Alpharetta, GA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/293,524**

(22) Filed: **Apr. 15, 1999**

Related U.S. Application Data

(63) Continuation-in-part of application No. 08/900,021, filed on Jul. 4, 1997, now Pat. No. 5,913,813.

(51) **Int. Cl.**[7] **A61N 5/00**
(52) **U.S. Cl.** **600/3**
(58) **Field of Search** 600/1–8

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,324,847 A	6/1967	Zoumboulis	.....	128/1.2
3,872,856 A	3/1975	Clayton	.....	128/1.2
4,417,576 A	11/1983	Baran	.....	128/207.15
4,706,652 A	11/1987	Horowitz	.....	128/1.2
4,754,745 A	7/1988	Horowitz	.....	128/1.2
4,763,642 A	8/1988	Horowitz	.....	128/1.2

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

EP	0340881	11/1989	..... A61N/5/10
EP	0867200	9/1998	
GB	2105201	3/1983	..... A61N/1/06
WO	9210932	7/1992	..... A61N/5/02
WO	9309724	5/1993	..... A61B/17/36
WO	9719723	6/1997	..... A61N/5/00
WO	9812979	4/1998	..... A61B/19/00
WO	9911325	3/1999	
WO	9933515	7/1999	
WO	9942163	9/1999	

OTHER PUBLICATIONS

A. Bex et al., *A System for Focal Intracavitary Irradiation of Bladder Cancer with Remote Iridium–192 Afterloading*, 21 Eur Urol 1992, 245–249 (1992).

Ashpole, R.D. et al., "A New Technique of Brachtherapy for Malignant Gliomas with Caesium–137: A New Method Utilizing a Remote Afterloading System," Clinical Oncology, vol. 2, 333–7 (1990).

Chun, M. et al., "Interstitial Iridium–192 Implantation for Malignant Brain Tumours. Part II: Clinical Experience," *The British Journal of Radiology*, vol. 62, 158–62 (1989).

Garfield, J. et al., "Postoperative Intracavitary Chemotherapy of Malignant Gliomas," *J. Neurosurg.*, vol. 39, 315–22 (Sep. 1973).

(List continued on next page.)

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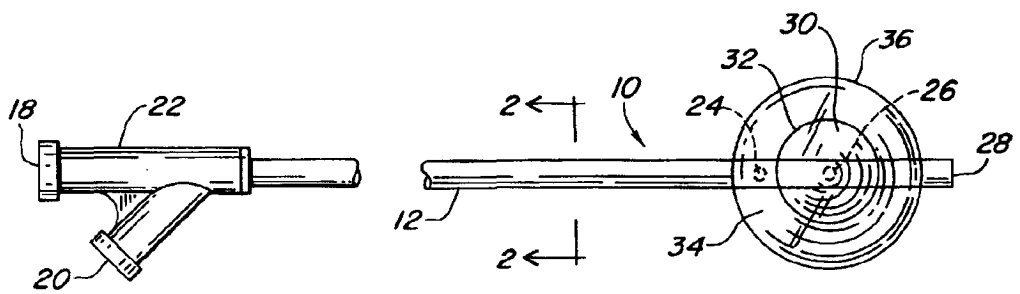
(57) **ABSTRACT**

An interstitial brachytherapy apparatus for delivering radioactive emissions to an internal body location includes a catheter body member having a proximal end and distal end, an inner spatial volume disposed proximate to the distal end of the catheter body member, an outer spatial volume defined by an expandable surface element disposed proximate to the distal end of the body member in a surrounding relation to the inner spatial volume, and a radiation source disposed in the inner spatial volume.

36 Claims, 3 Drawing Sheets



U.S. PATENT DOCUMENTS

4,821,725	A		4/1989	Azam et al. ..... 128/420 A
4,867,741	A		9/1989	Portnoy 604/10
5,084,001	A		1/1992	Van't Hooft et al. 600/3
5,084,015	A		1/1992	Moriuchi 604/96
5,106,360	A		4/1992	Ishiwara et al. 600/2
5,112,303	A		5/1992	Pudenz et al. 604/49
5,152,747	A		10/1992	Olivier 604/93
5,236,410	A		8/1993	Granov et al. 600/12
5,429,582	A		7/1995	Williams 600/2
5,484,384	A		1/1996	Fearnot 600/3
5,503,613	A		4/1996	Weinberger 600/3
5,566,221	A		10/1996	Smith et al. 378/145
5,611,767	A		3/1997	Williams 600/2
5,662,580	A		9/1997	Bradshaw et al. 600/3
5,707,332	A		1/1998	Weinberger 600/3
5,713,828	A		2/1998	Coniglione 600/7
5,720,717	A		2/1998	D'Andrea 604/21
5,764,723	A		6/1998	Weinberger et al. 378/65
5,782,742	A		7/1998	Crocker et al. 600/3
5,785,688	A		7/1998	Joshi et al. 604/141
5,913,813	A	*	6/1999	Williams et al. 600/3
5,924,973	A	*	7/1999	Wenberger 600/3
6,036,631	A		3/2000	McGrath et al. 600/3
6,059,812	A	*	5/2000	Clerc et al. 600/3

OTHER PUBLICATIONS

Gutin, P. et al., "Brachytherapy of Recurrent Malignant Brain Tumors With Removable High–Activity Iodine–125 Sources," *J. Neurosurg.*, vol. 60, 61–8 (1984).

Johannesen, T.B. et al., "Intracavity Fractionated Balloon Brachytherapy in Gilioblastoma," *Acta Neurochir (Wien)*, vol. 141, 127–33 (1999).

Leibel, S. et al., "The Integration of Interstitial Implantation Into the Preliminary Mangement of Patients With Malignant Gliomas: Results of a Phase II Northern California Oncology Group Trial," *Am. J. Clin. Oncol. (CCT)*, vol. 10, No. 2, p. 106 (1987).*

Roberts, D. et al., "Interstitial Hyperthermia and Iridium Brachytherapy in Treamtnet of Malignant Glioma," *J. Neurosurg.*, vol. 64, 581–7 (1986).*

Wu, A. et al., "Interstitial Iridium–192 Implantation for Malignant Brain Tumours, Part 1: Techniques of Dosimetry Planning," *The British Journal of Radiology*, vol. 62, 154–7 (1989).*

* cited by examiner

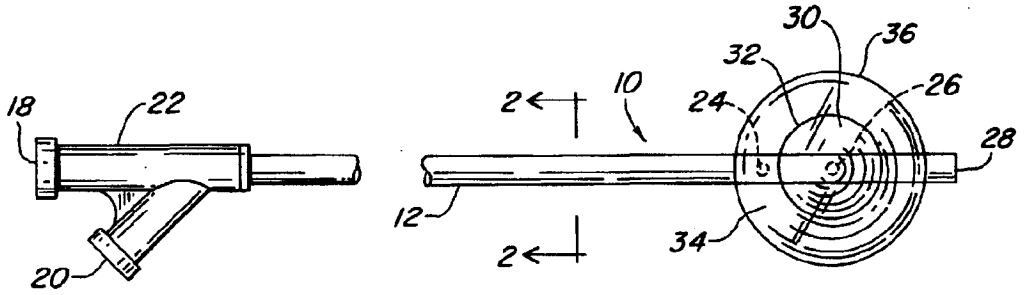


FIG. 1

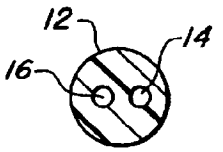


FIG. 2

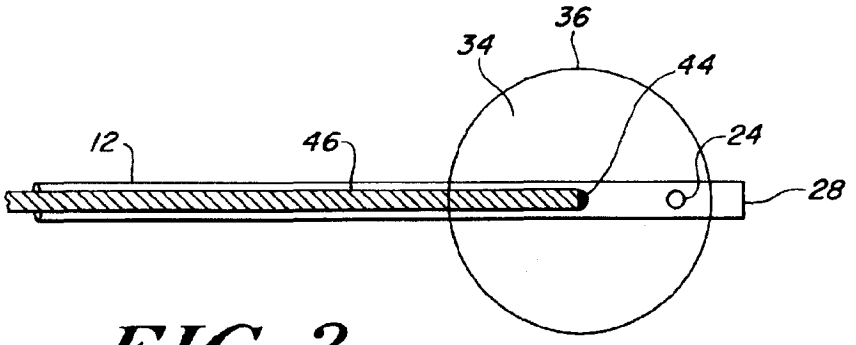


FIG. 3

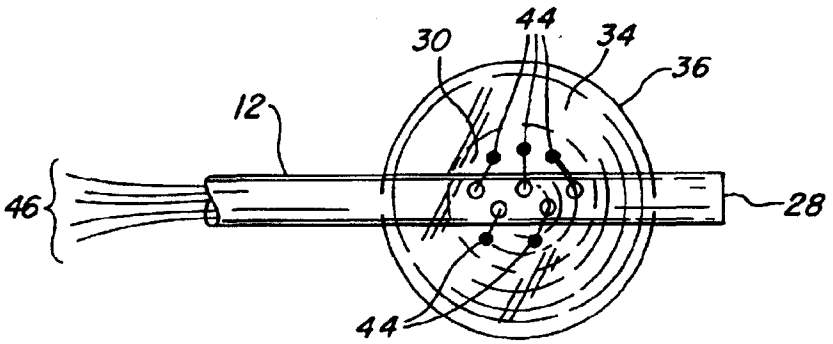


FIG. 4

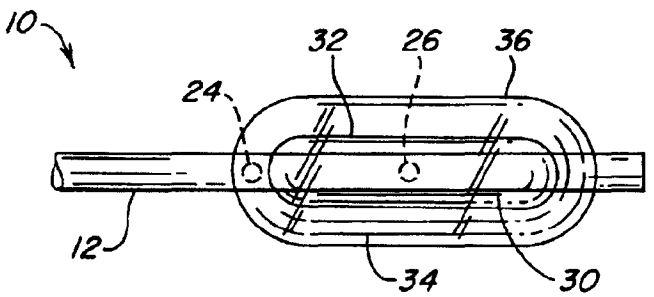


FIG. 5

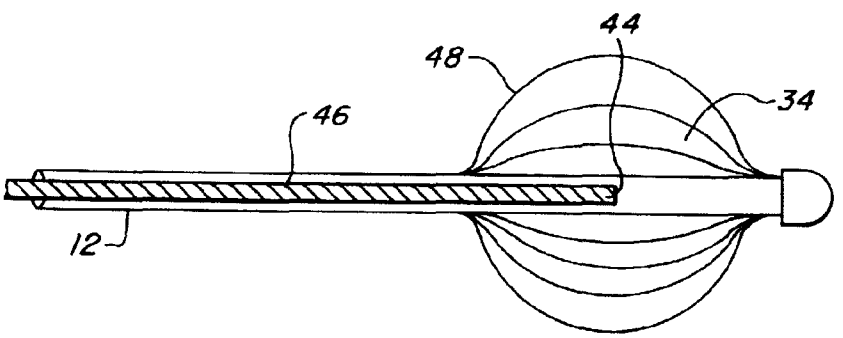


FIG. 6

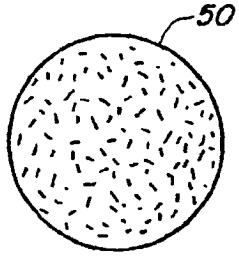


FIG. 7A

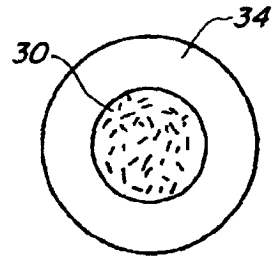


FIG. 7B

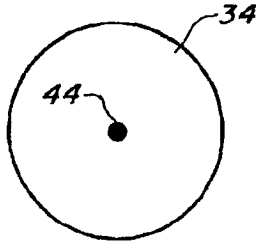


FIG. 7C

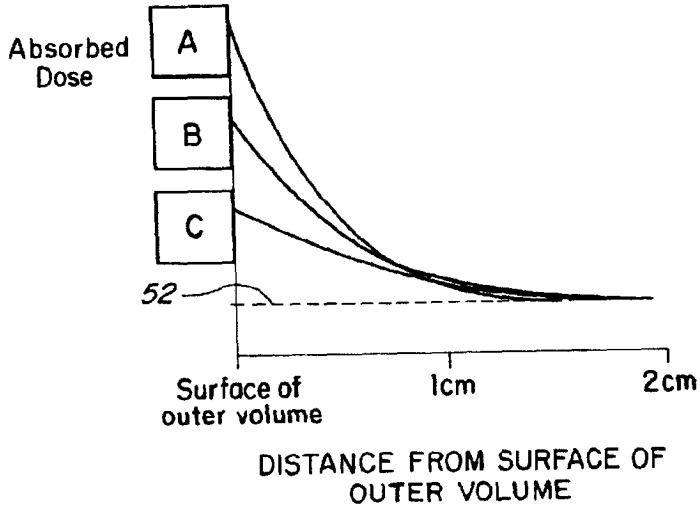


FIG. 7D

INTERSTITIAL BRACHYTHERAPY APPARATUS AND METHOD FOR TREATMENT OF PROLIFERATIVE TISSUE DISEASES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. patent application Ser. No. 08/900,021, filed Jul. 24, 1997, now U.S. Pat. No. 5,913,813 the contents of which are specifically incorporated herein by reference.

BACKGROUND OF THE INVENTION

The invention relates generally to apparatus for use in treating proliferative tissue disorders, and more particularly to an apparatus for the treatment of such disorders in the body by the application of radiation.

Malignant tumors are often treated by surgical resection of the tumor to remove as much of the tumor as possible. Infiltration of the tumor cells into normal tissue surrounding the tumor, however, can limit the therapeutic value of surgical resection because the infiltration can be difficult or impossible to treat surgically. Radiation therapy can be used to supplement surgical resection by targeting the residual tumor margin after resection, with the goal of reducing its size or stabilizing it. Radiation therapy can be administered through one of several methods, or a combination of methods, including external-beam radiation, stereotactic radiosurgery, and permanent or temporary interstitial brachytherapy. The term "brachytherapy," as used herein, refers to radiation therapy delivered by a spatially confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site. Owing to the proximity of the radiation source, brachytherapy offers the advantage of delivering a more localized dose to the target tissue region.

For example, brachytherapy is performed by implanting radiation sources directly into the tissue to be treated. Brachytherapy is most appropriate where 1) malignant tumor regrowth occurs locally, within 2 or 3 cm of the original boundary of the primary tumor site; 2) radiation therapy is a proven treatment for controlling the growth of the malignant tumor; and 3) there is a radiation dose-response relationship for the malignant tumor, but the dose that can be given safely with conventional external beam radiotherapy is limited by the tolerance or normal tissue. In brachytherapy, radiation doses are highest in close proximity to the radiotherapeutic source, providing a high tumor dose while sparing surrounding normal tissue. Interstitial brachytherapy is useful for treating malignant brain and breast tumors, among others.

Interstitial brachytherapy is traditionally carried out using radioactive seeds such as ^{125}I seeds. These seeds, however, produce inhomogeneous dose distributions. In order to achieve a minimum prescribed dosage throughout a target region of tissue, high activity seeds must be used, resulting in very high doses being delivered in some regions in proximity to the seed or seeds which can cause radionecrosis in healthy tissue.

Williams U.S. Pat. No. 5,429,582, entitled "Tumor Treatment," describes a method and apparatus for treating tissue surrounding a surgically excised tumor with radioactive emissions to kill any cancer cells that may be present in the tissue surrounding the excised tumor. In order to implement the radioactive emissions, Williams provides a catheter having an inflatable balloon at its distal end that defines a distensible reservoir. Following surgical removal of a tumor, the surgeon introduces the balloon catheter into the surgically created pocket left following removal of the tumor. The balloon is then inflated by injecting a fluid having one or more radionuclides into the distensible reservoir via a lumen in the catheter.

The apparatus described in Williams solves some of the problems found when using radioactive seeds for interstitial brachytherapy, but leaves some problems unresolved. The absorbed dose rate at a target point exterior to a radioactive source is inversely proportional to the square of the distance between the radiation source and the target point. As a result, where the radioactive source has sufficient activity to deliver a prescribed dose, say 2 centimeters into the target tissue, the tissue directly adjacent the wall of the distensible reservoir, where the distance to the radioactive source is very small, may still be overly "hot" to the point where healthy tissue necrosis may result. In general, the amount of radiation desired by the physician is a certain minimum amount that is delivered to a region up to about two centimeters away from the wall of the excised tumor. It is desirable to keep the radiation that is delivered to the tissue in the target treatment region within a narrow absorbed dose range to prevent over-exposure to tissue at or near the reservoir wall, while still delivering the minimum prescribed dose at the maximum prescribed distance from the reservoir wall.

There is still a need for an instrument which can be used to deliver radiation from a radioactive source to target tissue within the human body with a desired intensity and at a predetermined distance from the radiation source without over-exposure of body tissues disposed between the radiation source and the target.

SUMMARY OF THE INVENTION

The present invention solves the problems described above by providing an interstitial brachytherapy apparatus for delivering radioactive emissions to an internal body location. The apparatus includes a catheter body member having a proximal end and distal end, an inner spatial volume disposed proximate to the distal end of the catheter body member, an outer spatial volume defined by an expandable surface element disposed proximate to the distal end of the body member in a surrounding relation to the inner spatial volume, and a radiation source disposed in the inner spatial volume. The inner and outer spatial volumes are configured to provide an absorbed dose within a predetermined range throughout a target tissue. The target tissue is located between the outer spatial volume expandable surface and a minimum distance outward from the outer spatial volume expandable surface. The predetermined dose range is defined as being between a minimum prescribed absorbed dose for delivering therapeutic effects to tissue that may include cancer cells, and a maximum prescribed absorbed dose above which healthy tissue necrosis may result.

In different embodiments, the inner spatial volume can be defined by a distensible polymeric wall containing radioactive source material which can be a fluid material, by a solid radioactive source, or by a region containing a plurality of solid radioactive sources. The outer spatial volume is defined by an expandable surface element that may be, for example, an inflatable polymeric wall or an expandable cage. The expandable surface element can cause tissue to conform to its intended shape, and preferably, the apparatus creates absorbed isodose profiles in the target tissue that are substantially similar in shape to the expandable surface element in substantially three dimensions.

The invention also provides a method for treating a proliferating tissue disease using interstitial brachytherapy at an internal body location. The method includes surgically creating access to the proliferating tissue within a patient and surgically resecting at least a portion of the proliferating tissue to create a resection cavity within body tissue. An interstitial brachytherapy apparatus for delivering radioactive emissions as described above is then provided and intra-operatively placed into the resection cavity. After a prescribed absorbed dose has been delivered to tissue surrounding the apparatus, the apparatus is removed. The radioactive source material may be placed into the interstitial brachytherapy apparatus after the apparatus is placed in the resection cavity, and may be removed before the apparatus is removed. The method has particular applications to brain and breast cancers.

DESCRIPTION OF THE DRAWINGS

The foregoing features, objects and advantages of the invention will become apparent to those skilled in the art from the following detailed description of a preferred embodiment, especially when considered in conjunction with the accompanying drawings in which:

FIG. **1** is a side view of an interstitial brachytherapy apparatus of the invention for delivering radioactive emissions to body tissue;

FIG. **2** is a cross-sectional view taken along the line **2—2** in FIG. **1**;

FIG. **3** is an additional embodiment of an interstitial brachytherapy apparatus of the invention having a solid radiation source;

FIG. **4** is an additional embodiment of an interstitial brachytherapy apparatus of the invention having a radiation source comprising a plurality of solid radiation particles;

FIG. **5** depicts a further embodiment of the invention wherein the inner and outer spatial volumes of the interstitial brachytherapy apparatus are non-spherical;

FIG. **6** illustrates an interstitial brachytherapy apparatus of the invention having an expandable outer spatial volume surface; and

FIGS. **7**A–D illustrate the absorbed dose versus distance into target tissue for several interstitial brachytherapy apparatus configurations.

DESCRIPTION OF THE PREFERRED EMBODIMENT

A surgical instrument **10** for providing radiation treatment to proliferative tissue in a living patient is illustrated in FIG. **1**. Surgical instrument **10** includes a tubular body member **12** having first and second lumens **14** and **16** (FIG. **2**) extending from proximal ports **18** and **20** in a molded plastic hub **22** to inflation ports **24** and **26** formed through the side wall of the tube **12** and intersecting with the lumens **14** and **16**, respectively.

Affixed to the tubular body **12** proximate the distal end **28** thereof is an inner spatial volume **30** which may be defined by a generally spherical polymeric film wall **32**. The interior of the inner volume **30** is in fluid communication with the inflation port **26**. Surrounding inner spatial volume **30** is an outer spatial volume **34** defined by an outer polymeric film wall **36** that is appropriately spaced from the wall **32** of the inner spatial volume **30** when the two volumes are inflated or otherwise supported. Outer volume **34** encompasses inflation port **24**. With no limitation intended, the distensible polymeric film walls may comprise a biocompatible, radiation resistant polymer, such as silastic rubbers, polyurethanes, polyethylene, polypropylene, polyester, or PVC.

The embodiment of FIG. **1** includes inner and outer spatial volumes **30** and **34**, one inside the other. The outer spatial volume **34**, being the volume defined by the space between the inner spherical wall **32** and the outer spherical wall **36**, may be filled with air or, alternatively, a radiation absorbing fluid, such as a contrast media used in angiography. The inner volume **30** is then filled with a material containing a predetermined radionuclide, for example, I-125, I-131, Yb-169 or other source of radiation, such as radionuclides that emit photons, beta particles, gamma radiation, or other therapeutic rays. The radioactive material contained within the inner chamber **32** can be a fluid made from any solution of radionuclide(s), e.g., a solution of I-125 or I-131. A radioactive fluid can also be produced using a slurry of a suitable fluid containing small particles of solid radionuclides, such as Au-198, Y-90. Moreover, the radionuclide(s) can be embodied in a gel. One radioactive material useful in the invention is Iotrex™, a sterile single use, non-pyrogenic solution containing sodium 3-(^{125}I)iodo-4-hydroxybenzenesulfonate (^{125}I-HBS), available from Proxima Therapuetics, Inc. of Alpharetta, Ga.

As an alternative method of providing radioactive source material, such material may be coated on, chemically bonded to, or copolymerized with the material forming inner spherical wall **32**.

Where the radioactive source material is provided as a fluid or gel within inner spherical wall **32**, it may be desirable to provide a solid outer spherical wall **36**. Should inner spherical wall **32** rupture, the radioactive source material will be retained within outer spherical wall **36** and will not leak into the patient. For further safety, the burst strength of inner spherical wall **32** may be designed so as to be lower than that of outer spherical wall **36**. In this way, inner spherical wall **32** will rupture under stress first, releasing its contents into the larger combined space of the inner and outer volumes **30**, **34** and releasing any pressure built up within the inner spherical wall **32** and reducing the risk that radioactive material will spill into the patient. In the event of such a rupture, radioactive fluid could be drained from the apparatus through port **24** by way of lumen **14**, and also from port **26** by way of lumen **16**.

In a further embodiment, illustrated in FIG. **3**, instead of having the inner spatial volume **30** defined by a generally spherical polymeric film wall as at **32**, the catheter body member **12** may have a solid spherical radiation emitting material **44** as the inner spatial volume **30**. For example, radioactive micro spheres of the type available from the 3M Company of St. Paul, Minn., may be used. This radioactive source can either be preloaded into the catheter at the time of manufacture or loaded into the device after it has been implanted into the space formerly occupied by the excised tumor. The solid radiation emitting material **44** can be inserted through catheter **12** on a wire **46**, for example, using an afterloader (not shown). Such a solid radioactive core configuration offers an advantage in that it allows a wider range of radionuclides than if one is limited to liquids. Solid radionuclides that could be used with the delivery device of the present invention are currently generally available as brachytherapy radiation sources. In this embodiment solid spherical inner spatial volume **30** is surrounded by outer spherical wall **36**, defining outer spatial volume **34** between the outer spherical wall **36** and the inner spatial volume **30** with the outer spatial volume **34** occupied by a radioactive ray absorbent material, such as air, water or a contrast material.

In a further embodiment, illustrated in FIG. 4, inner spatial volume **30**, instead of comprising a single solid sphere, may comprise a plurality of radiation emitting particles **44** strategically placed within the inner spatial volume **30** so as to radiate in all directions with a substantially equal intensity. This plurality of radiation emitting particles **44** can be mounted on the distal ends of a plurality of wires **46** that are routed through the catheter body **12** and exit a plurality of ports formed through the wall of the catheter body and reaching the lumen. This arrangement allows the exact positioning of the individual radiation sources **44** to be positioned so as to generate a desired resultant profile.

As illustrated in FIG. **5**, it is not essential to the invention that the volumes **30** and **34** have spherical walls, so long as the resultant dosing profile is consistent with the shape of the outer volume **34**. That is, the absorbed dose within the target tissue at points equidistant from the surface **36** of the outer spatial volume **34** should be substantially uniform in substantially every direction. Put another way, the three dimensional isodose profiles generated by the radiation source should be substantially similar in shape to the outer spatial volume **34**. Where the inner and outer spatial volumes are created by inflatable membranes and one of the volumes contains a fluid radiation source, this can be achieved by ensuring that the spacing between the wall of the inner volume and the wall of the outer volume remain generally constant. In either the concentric spherical embodiment of FIG. **1** or the non-spherical configuration of FIG. **5**, this result can be achieved by careful placement of precision blown or molded polymer partitions or by using compressible foams or mechanical spacers in the form of webs joining the inner wall **32** to the outer wall **36**. The desired isodose profiles conforming to the shape of the outer spatial volume **34** can also be obtained, for example, by strategic placement of a plurality of radioactive particle sources within the inner spatial volume **30**. Where the apparatus of the invention is deployed in soft tissue, it may also be important for the surface **36** of the outer spatial volume **34** to be sufficiently firm so as to force the target tissue to take on the shape of the surface **36** so that the desired relationship between the isodose profiles and the target tissue is achieved.

When used in an interstitial application, the surface of the outer spatial volume **34** must establish a relationship between the inner spatial volume **30** and the target tissue so as to achieve the aforementioned isodose profile, however, the surface of the outer volume need not be a solid material. For example, as illustrated in FIG. **6**, the surface of the outer volume **34** could be an expandable cage **48** formed from a shape memory metal, such as nitinol, or a suitable plastic, such as an expandable polyethylene cage. Such a cage can be formed in the desired shape to conform to a particular isodose profile, then be contracted for delivery to the target site in vivo, then expanded to cause the tissue surrounding the surgically resected region to take the appropriate shape. The size of the outer spatial volume **34** generally will correspond approximately to the amount of tissue resected, or be slightly larger, allowing the expandable surface of the outer spatial volume to urge tissue on the surface of the resected region into the appropriate shape to promote an even dose distribution around the outer spatial volume in the target tissue. In typical applications, the outer spatial volume has a diameter of approximately 2 to 4 centimeters. In these same applications, where the radiation source is provided as a fluid within an inner balloon, the inner balloon generally has a diameter of approximately 0.5 to 3 centimeters.

FIGS. 7A–D illustrate the ability of an interstitial brachytherapy apparatus of the invention to deliver a minimum prescribed dose within target tissue while avoiding necrosis inducing radiation "hot spots" in tissue proximate to the apparatus. FIG. **7A** illustrates an interstitial brachytherapy apparatus (device A) such as those employed in U.S. Pat. No. 5,429,582, having a single spatial volume **50** filled with a radioactive material in solution. FIG. **7B** illustrates an interstitial brachytherapy apparatus (device B) of the invention having a first, inner spatial volume **30** filled with a radioactive material in solution and defined by membrane **32**, and a second, outer spatial volume **34** defined by membrane **36** that is substantially evenly spaced apart from membrane **32** in substantially three dimensions. FIG. **7C** illustrates an additional interstitial brachytherapy apparatus (device C) of the invention having a solid, spherical radiation source **44** as the inner spatial volume and a spherical outer spatial volume **34** defined by membrane **36**.

Each of the devices illustrated in FIGS. **7A–C** can be configured to deliver a substantially uniform dose at a given distance into the target tissue from the surface of the outer spatial volume **34** (or from single spatial volume **50** for device A) and to deliver a minimum prescribed dose within a given prescribed depth range into the tissue from the surface of the outer spatial volume **34**. However, the different devices provide very different dose profiles as a function of distance from the surface of the outer volume as illustrated in FIG. **7D**. FIG. **7D** plots the absorbed dose at a given distance into the target tissue from the surface of the outer spatial volume **34** for each of the devices A, B, and C.

Each device can deliver a minimum prescribed dose **52** at a given distance from the surface of the outer spatial volume. For example, device A can readily be configured to provide a dose in a therapeutic range, say between 40 to 60 Gray, at a distance between 0.5 and 1.0 cm from the outer spatial volume for an outer spatial volume having a diameter of 4.0 cm and being in contact with the resection cavity wall. In a typical embodiment, the radioactive source material ranges from approximately 150 to 450 mCi in activity and encompasses most of the target treatment area with a 0.4 to 0.6 Gray/hour isodose contour. At this treatment rate, treatment may be completed in approximately 3 to 7 days, or more commonly, in approximately 3 to 5 days.

In order to reach the minimum prescribed dosage at this distance, however, device A must provide a dose proximate to the surface of the outer spatial volume that is substantially larger than the minimum prescribed dose. For the 4.0 cm diameter outer spatial volume example, the absorbed dosage would be approximately 131 Gray at the outer spatial volume surface. Ideally, radiation therapy should make use the inherent difference in radiosensitivity between the tumor and the adjacent normal tissues to destroy cancerous tissue while causing minimal disruption to surrounding normal tissues. At high doses of radiation, however, the percentage of exposed cells that survive treatment decreases with first-order kinetics in proportion to increasing radiation dose. With increasing cell death comes increasing risk of necrosis or tissue death in healthy tissue that is treated with a high dose of radiation. Accordingly, it is desirable to keep the maximum radiation dose delivered by the brachytherapy apparatus as low as possible while still delivering the desired therapeutic dose to the desired range of tissue.

Comparing the plots A, B, and C, the absorbed dose profile in the space between the 2 cm site and the surface of the outer spatial volume for the devices of the invention is maintained in a much narrower range, preventing over-treatment of body tissue at or close to the surface of the outer volume of the device. Because devices B and C provide an outer spatial volume **34** between the radioactive source and

the target tissue, these devices can use hotter radiation sources to reach the minimum prescribed dosage, but take advantage of the distance between the radioactive source and the target tissue provided by the outer spatial volume **34** to reduce or eliminate hot spots in the target tissue.

Returning to the 4.0 cm diameter outer spatial volume example, if the radiation source is contained within an inner spatial volume, say a solid radioactive sphere such as device C, the absorbed dose profile becomes much different. If the radiation source is configured to provide the same 60 Gray dose at 0.5 cm into the target tissue, the absorbed dose at the outer spatial volume surface is only 94 Gray—a significant decrease from the 131 Gray dose for a type A device. In addition, the treatment range for the type C device will be extended under these circumstance as compared to the type A device, delivering a 40 Gray dose beyond 1.0 cm into the target tissue and delivering approximately double the dose at 3.0 cm into the target tissue. In one embodiment, the inner and outer spatial volumes are configured to control the absorbed dose at the outer spatial volume surface so that the absorbed dose is no greater than about 100 Gray while providing a therapeutic absorbed dose into the target tissue at the desired range. The capability of the apparatus of the invention to deliver absorbed doses deeper into the target tissue than prior interstitial brachytherapy devices while controlling the dose in proximity to the apparatus to reduce or eliminate the risk of healthy tissue necrosis allows for the use of brachytherapy in a greater number of cases.

The interstitial brachytherapy apparatus of the invention can be used in the treatment of a variety of malignant tumors, and is especially useful for in the treatment of brain and breast tumors.

Many breast cancer patients are candidates for breast conservation surgery, also known as lumpectomy, a procedure that is generally performed on early stage, smaller tumors. Breast conservation surgery is typically followed by postoperative radiation therapy. Studies report that 80% of breast cancer recurrences after conservation surgery occur near the original tumor site, strongly suggesting that a tumor bed "boost" of local radiation to administer a strong direct dose may be effective in killing any remaining cancer and preventing recurrence at the original site. Numerous studies and clinical trials have established equivalence of survival for appropriate patients treated with conservation surgery plus radiation therapy compared to mastectomy.

Surgery and radiation therapy are the standard treatments for malignant solid brain tumors. The goal of surgery is to remove as much of the tumor as possible without damaging vital brain tissue. The ability to remove the entire malignant tumor is limited by its tendency to infiltrate adjacent normal tissue. Partial removal reduces the amount of tumor to be treated by radiation therapy and, under some circumstances, helps to relieve symptoms by reducing pressure on the brain.

A method according to the invention for treating these and other malignancies begins by surgical resection of a tumor site to remove at least a portion of the cancerous tumor and create a resection cavity. Following tumor resection, but prior to closing the surgical site, the surgeon intraoperatively places an interstitial brachytherapy catheter apparatus, having an inner spatial volume and an outer spatial volume as described above but without having the radioactive source material loaded, into the tumor resection cavity. Once the patient has sufficiently recovered from the surgery, the interstitial brachytherapy catheter is loaded with a radiation source. The radioactive source dwells in the catheter until the prescribed dose of radiotherapy is delivered, typically for approximately a week or less. The radiation source is then retrieved and the catheter is removed. The radiation treatment may end upon removal of the brachytherapy apparatus, or the brachytherapy may be supplemented by further doses of radiation supplied externally.

It will be understood that the foregoing is only illustrative of the principles of the invention, and that various modifications can be made by those skilled in the art without departing from the scope and spirit of the invention. All references cited herein are expressly incorporated by reference in their entirety.

What is claimed is:

1. An interstitial brachytherapy apparatus for delivering radioactive emissions to an internal body location comprising:

(a) a catheter body member having a proximal end and distal end;

(b) an inner spatial volume disposed proximate to the distal end of the catheter body member;

(c) an outer spatial volume defined by an expandable surface element disposed proximate to the distal end of the body member in a surrounding relation to the inner spatial volume; and

(d) a radiation source disposed in the inner spatial volume and generating a three-dimensional isodose profile that is substantially similar in shape to the expandable surface element.

2. The apparatus of claim **1**, wherein the inner and outer spatial volumes are configured to provide a minimum prescribed absorbed dose for delivering therapeutic effects to a target tissue, the target tissue being defined between the outer spatial volume expandable surface and a minimum distance outward from the outer spatial volume expandable surface, the apparatus providing a controlled dose at the outer spatial volume expandable surface to reduce or prevent necrosis in healthy tissue proximate to the expandable surface.

3. The apparatus of claim **2**, wherein a predetermined spacing is provided between said inner spatial volume and the expandable surface element.

4. The apparatus of claim **3**, wherein the expandable surface element is adapted to contact tissue surrounding a resected cavity and adapted to conform the tissue to the desired shape of the expandable surface element.

5. The apparatus of claim **2**, wherein the minimum prescribed absorbed dose is 40 Gray at a distance of at least one centimeter from the expandable surface element.

6. The apparatus of claim **5**, wherein the dose rate in at least a portion of the target tissue is between about 0.4 and 0.6 Gray/hour.

7. The apparatus of claim **5**, wherein the maximum absorbed dose delivered to the target tissue is less than 100 Gray.

8. The apparatus of claim **2**, wherein the outer spatial volume has a diameter between about two and four centimeters.

9. The apparatus of claim **2**, wherein the inner spatial volume is an inner closed, distensible chamber defined by a further radiation transparent wall.

10. The apparatus of claim **9**, wherein the radioactive source is in a fluid form.

11. The apparatus of claim **10**, wherein the expandable surface element is a solid distensible surface and the outer spatial volume is a closed, distensible chamber and the expandable surface element is a radiation transparent wall.

12. The apparatus of claim 11, wherein a burst strength of the distensible chamber defining the outer spatial volume is greater than a burst strength of the chamber defining the inner spatial volume.

13. The apparatus of claim 1, wherein the expandable surface element is an expandable cage.

14. The apparatus of claim 13, wherein the expandable cage comprises a shape memory material.

15. The apparatus of claim 14, wherein the expandable cage comprises nitinol.

16. The apparatus of claim 1, wherein the radiation source is a solid radiation source.

17. The apparatus of claim 1, wherein the radiation source is a plurality of solid radiation sources arranged to provide an isodose profile having a shape substantially similar to the shape of the outer spatial volume.

18. The apparatus of claim 2, wherein the prescribed absorbed dose is delivered to the target tissue in substantially three dimensions.

19. A method for treating a proliferating tissue disease using interstitial brachytherapy at an internal body location comprising:

(a) surgically creating access to the proliferating tissue in a patient;

(b) surgically resecting at least a portion of the proliferating tissue to create a resection cavity within body tissue;

(c) providing an interstitial brachytherapy apparatus for delivering radioactive emissions comprising:

(i) a catheter body member having a proximal end and distal end;

(ii) an inner spatial volume disposed proximate to the distal end of the catheter body member;

(iii) an outer spatial volume defined by an expandable surface element disposed proximate to the distal end of the body member in a surrounding relation to the inner spatial volume; and

(iv) a radiation source disposed in the inner spatial volume and generating a three-dimensional isodose profile that is substantially similar in shape to the expandable surface element;

(d) intraoperatively placing the interstitial brachytherapy apparatus into the resection cavity until a prescribed absorbed dose has been delivered to tissue surrounding the apparatus; and

(e) removing the interstitial brachytherapy apparatus.

20. The method of claim 19, further including placing the radioactive source into the interstitial brachytherapy apparatus after the step of placing the apparatus into the tumor resection cavity.

21. The method of claim 19, further including removing the radioactive source from the interstitial brachytherapy apparatus before the step of removing the apparatus.

22. The method of claim 19, wherein the proliferating tissue is a patient's brain.

23. The method of claim 19, wherein the proliferating tissue is a patient's breast.

24. The method of claim 19, further including configuring the inner and outer spatial volumes to provide a minimum prescribed absorbed dose for delivering therapeutic effects to a target tissue, the target tissue being defined between the outer spatial volume expandable surface and a minimum distance outward from the outer spatial volume expandable surface, the apparatus providing a controlled dose at the outer spatial volume expandable surface to reduce or prevent necrosis in healthy tissue proximate to the expandable surface.

25. The method of claim 24, further including providing a predetermined spacing between said inner spatial volume and the expandable surface element.

26. The method of claim 25, wherein the expandable surface element is adapted to contact tissue surrounding a resected cavity and adapted to conform the tissue to the desired shape of the expandable surface element.

27. The method of claim 24, wherein the minimum prescribed absorbed dose is 40 Gray at a distance of at least one centimeter from the expandable surface element.

28. The method of claim 27, wherein the dose rate in at least a portion of the target tissue is between about 0.4 and 0.6 Gray/hour.

29. The method of claim 27, wherein the maximum absorbed dose delivered to the target tissue is less than 100 Gray.

30. The method of claim 24, wherein the outer spatial volume has a diameter between about two and four centimeters.

31. The method of claim 24, wherein the step of configuring the inner and outer spatial volumes includes expanding the inner and outer spatial volumes.

32. A method for treating a proliferating tissue disease using interstitial brachytherapy at an internal body location comprising:

(a) surgically creating access to the proliferating tissue in a patient;

(b) surgically resecting at least a portion of the proliferating tissue to create a resection cavity within body tissue;

(c) providing an interstitial brachytherapy apparatus for delivering radioactive emissions comprising:

(i) a catheter body member having a proximal end and distal end;

(ii) an inner spatial volume disposed proximate to the distal end of the catheter body member;

(iii) an outer spatial volume defined by an expandable surface element disposed proximate to the distal end of the body member in a surrounding relation to the inner spatial volume; and

(iv) a radiation source disposed in the inner spatial volume;

(d) intraoperatively placing the interstitial brachytherapy apparatus into the resection cavity;

(e) configuring the inner and outer spatial volumes to provide a minimum prescribed absorbed dose for delivering therapeutic effects to a target tissue, the target tissue being defined between the outer spatial volume expandable surface and a minimum distance outward from the outer spatial volume expandable surface, the apparatus providing a controlled dose at the outer spatial volume expandable surface to reduce or prevent necrosis in healthy tissue proximate to the expandable surface; and

(f) removing the interstitial brachytherapy apparatus.

33. The method of claim 32, wherein the step of configuring the inner and outer spatial volumes includes expanding the inner and outer spatial volumes.

34. A method for treating a proliferating tissue disease using interstitial brachytherapy at an internal body location comprising:

(a) surgically creating access to the proliferating tissue in a patient;

(b) surgically resecting at least a portion of the proliferating tissue to create a resection cavity within body tissue;

(c) providing an interstitial brachytherapy apparatus for delivering radioactive emissions comprising:

(i) a catheter body member having a proximal end and distal end;

(ii) an inner spatial volume disposed proximate to the distal end of the catheter body member;

(iii) an outer spatial volume defined by an expandable surface element disposed proximate to the distal end of the body member in a surrounding relation to the inner spatial volume; and

(iv) a radiation source disposed in the inner spatial volume;

(d) intraoperatively placing the interstitial brachytherapy apparatus into the resection cavity;

(e) adapting the expandable surface element to contact tissue surrounding the resection cavity to conform the tissue to the desired shape of the expandable surface element;

(f) delivering a prescribed absorbed dose to tissue surrounding the apparatus; and

(g) removing the interstitial brachytherapy apparatus.

35. The method of claim **34**, wherein the step of adapting the expandable surface element includes expanding the outer surface volume.

36. An interstitial brachytherapy apparatus for delivering radioactive emissions to an internal body location comprising:

(a) a catheter body member having a proximal end and distal end;

(b) an inner spatial volume disposed proximate to the distal end of the catheter body member;

(c) an outer spatial volume defined by an expandable surface element disposed proximate to the distal end of the body member in a surrounding relation to the inner spatial volume; and

(d) a radiation source disposed in the inner spatial volume;

wherein the inner and outer spatial volumes are configured to provide a minimum prescribed absorbed dose for delivering therapeutic effects to a target tissue, the target tissue being defined between the outer spatial volume expandable surface and a minimum distance outward from the outer spatial volume expandable surface, the apparatus providing a controlled dose at the outer spatial volume expandable surface to reduce or prevent necrosis in healthy tissue proximate to the expandable surface.

* * * * *

Exhibit 5

Clinical Oncology (1990) 2:333–337

Clinical Oncology

Original Article

A New Technique of Brachytherapy for Malignant Gliomas with Caesium-137: A New Method Utilizing a Remote Afterloading System*

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Abstract. Failure of conventional treatment to cure malignant gliomas has stimulated interest in various forms of brachytherapy. We describe a new method of using intracranial radiation utilizing a remotely-controlled afterloading system with a modified endotracheal tube as the applicator. The system used is the Selectron LDM/MDR (Nucleotron) which is a sophisticated machine widely available at radiotherapy centres and primarily used to treat gynaecological malignancies. It uses Caesium-137 in the form of spherical pellets in a linear source train within a sealed system. The applicator is implanted at the time of surgical resection. The inflated balloon stabilises the applicator and allows a suitable dose distribution at a distance from the source train to be achieved. Details of the implantation and radiation procedures as well as the dosimetry calculation are presented. The advantages are simplicity of use, the elimination of radiation risk to personnel and the combination of cytoreduction and applicator implantation in one surgical procedure.

Keywords: Malignant glioma; Brachytherapy; Caesium-137; Remote afterloading

INTRODUCTION

Conventional treatment does not cure malignant gliomas. Therapeutic failure is wholly attributable to the inability of surgery and external beam radiotherapy to locally eradicate tumour cells, with nine out of ten recurrences occurring within the margins of the original tumour (Hochberg and Pruitt, 1980).

Ionizing radiation is effective in prolonging survival (Salcman, 1980), with a linear correlation between radiation dose and length of survival (Walker *et al.*, 1979), but the limited tolerance of normal brain has restricted the maximum permissible dose to about 55–60 Gy (Leibel and Sheline, 1987). This has stimulated interest in different ways of increasing therapeutic effectiveness (Gutin *et al.*, 1984; Sewchand *et al.*, 1984; Murray *et al.*, 1986; Saleman *et al.*, 1986) including adjuvant modalities such as hyperthermia and radiosensitizers (Nelson *et al.*, 1986; Roberts *et al.*, 1986).

Caesium-137 has already been used to treat brain tumours in a stereotactically implanted and afterloaded applicator (Mantell *et al.*, 1986). We now describe a new form of brachytherapy utilizing Caesium-137 in a remote afterloading system with a modified endotracheal tube as the applicator. It can be used to irradiate the tumour bed following surgical resection of the tumour. It may be used alone or in combination with external beam irradiation. The advantages are simplicity of use, elimination of radiation risk to personnel and the avoidance of salvage craniotomy for mass effect caused by late radionecrosis as experienced in brachytherapy methods using wire implants. Only one surgical procedure is needed as the applicator is implanted under direct vision at the time of the cytoreductive operation.

* The authors wish to dedicate this paper to the late Dr Trevor Godden, Principal Physicist, Bristol Radiotherapy and Oncology Centre.

Correspondence and offprint requests to: Mr H. B. Coakham, Imperial Cancer Research Fund Paediatric and Neuro-Oncology Laboratory, Frenchay Hospital, Bristol BS16 1LE, UK.

In this pilot study, the feasibility of Caesium-137 brachytherapy was assessed in cases of malignant glioma that had relapsed following initial conventional therapy by surgery and external irradiation.

MATERIALS AND METHODS

Patient Selection

Patients were evaluated at a joint Neurosurgical/Oncological clinic. Criteria for inclusion were recurrent supratentorial malignant gliomas (Kernohan grade 3/4) where the tumours were judged to be accessible through a standard craniotomy on the evidence of CT and/or MRI scans. All these patients had full conventional therapy initially in the form of surgery and radiotherapy to a dose of 46-60 Gy given in five fractions per week over 4-6 weeks.

Apparatus

We used a remotely controlled afterloading system, the Selectron LDR/MDR (Nucletron). This is a 3–6 channel low/medium dose rate system installed as part of a purpose-built suite at the Radiotherapy Centre. Although it is mostly used for gynaecological cancers, no adaptation is necessary when treating gliomas.

The source container, transfer and control systems are all housed in the same unit from where the source train, which is made up of active and inactive spherical pellets, can be programmed to deliver the required dose. The radionuclide used is Caesium-137, contained in an active bead of 1.5 mm size and encapsulated in stainless steel to form a sphere with an outside diameter of 2.5 mm. These beads have a nominal activity of 1.4 GBq each.

The sources are pneumatically transferred into a standard selectron applicator (outside diameter 7.0 mm) which in turn fits snugly into the intracranial applicator that has been implanted surgically. This applicator is the only unusual piece of equipment and is an endotracheal tube (Portex, Blue Line, i.d. 8.0 with a Profile cuff) which has been shortened to 20 cm with the distal end sealed off just beyond the lower end of the balloon (Fig. 1).

Implantation Procedure

After routine investigation all patients underwent repeat craniotomy via the original osteoplastic flap.

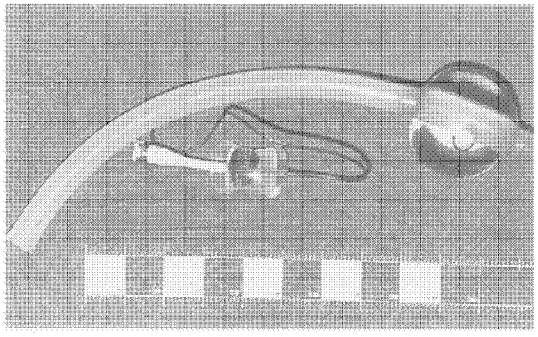

Fig. 1. The modified catheter with the sealed distal end and inflated balloon.

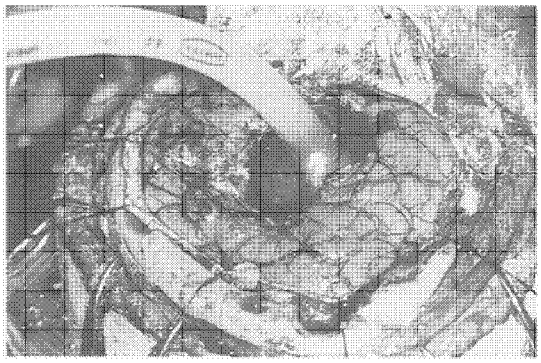

Fig. 2. The tumour cavity at operation with the modified catheter held in situ by the inflated balloon.

Cytoreduction remained the first aim and as much tumour was removed as deemed safe. The modified catheter was then inserted under direct vision so that the inflated balloon filled the postsurgical cavity, and the stem was brought out through one of the existing burr-holes (Fig. 2).

The balloon was filled with radio-opaque contrast medium (Conray 280 diluted to 2% strength with normal saline) to facilitate later X-ray visualization and dosimetry calculations. The volume to be used varies according to the size of the tumour bed, but a typical case needed 15 ml to give a balloon diameter of 2.9 cm. The scalp was closed tightly around the emerging tube and a padded head dressing applied. Routine antibiotic and steroid cover were given, consisting of Cefuroxime 1.5 g peroperatively and then 750 mg tds for three days, and Dexamethasone 4 mg tds and then reduced as and when possible.

The patient was then transferred to the Radiotherapy Centre for further treatment. No problems were encountered with this 'between hospital' transfer and patients tolerated it fairly well.

DOSIMETRY CALCULATION

After the patient had been transferred to the radiotherapy centre the 'Selectron' applicator was manually fitted into the protruding intracranial applicator, ensuring that the tip was right down to the base, and then marked on the outside to ensure accurate repositioning after the source localization procedure. A dummy source train was positioned in the applicator prior to taking localizing radiographs. These were AP and lateral skull radiographs incorporating the double ring method to determine magnification factor (Fig. 3).

The dose distribution is calculated from the above data on a Data General Eclipse computer system using in-house software. The plastic applicator and fluid in the balloon are soft tissue equivalent with regard to absorbed radiation dose and no additional factor is used in the dose calculation.

We aim to produce a mean dose rate of about 250 cGy/h at a distance of 0.5 cm from the balloon's surface for a total of about 20 h to give a total dosage of 50 Gy to the tumour bed. This is computed by varying the position of active and inactive beads in the source train until a satisfactory isodose curve to match the cavity shape is found (Fig. 3). In a typical case this is achieved by about a dozen active sources.

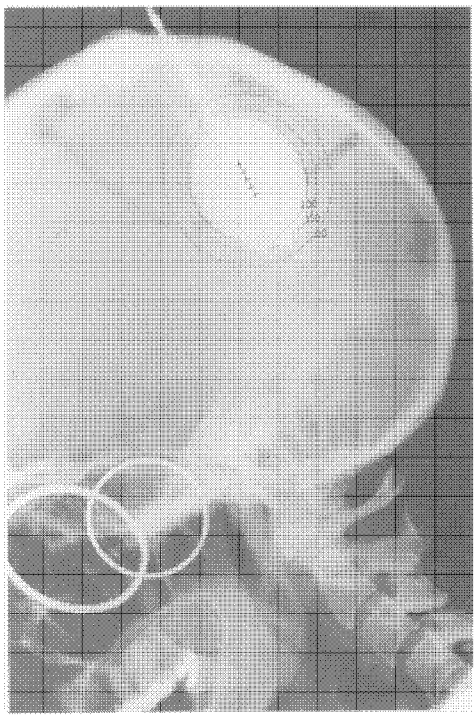

Fig. 3. Lateral radiograph showing the double ring method of magnification calculation, and Isodose curves computed around a dummy source train in the balloon.

RADIATION ADMINISTRATION PROCEDURE

This takes place in a purpose built suite comprising a private room for the patient with the Selectron equipment housed in an adjacent ante-room. The source delivery tubes pass through the wall and are fixed next to the patient's bed.

After removal of the dummy source train, the patient is connected to the machine via a treatment tube and the Selectron programmed to deliver the required dose. Treatment usually consisted of 3–4 hour periods with meal, visiting and overnight breaks as convenient, although the treatment was not divided into 'fractions' in the usual sense. Total treatment time varied from 15 to 20 hours and this could usually be completed within 48 hours.

Throughout the treatment periods the patients are attached to the machine and confined to bed (Fig. 4). In between these periods they are totally unrestrained and can carry out all activities of daily living. Nursing procedures continue in the normal way with

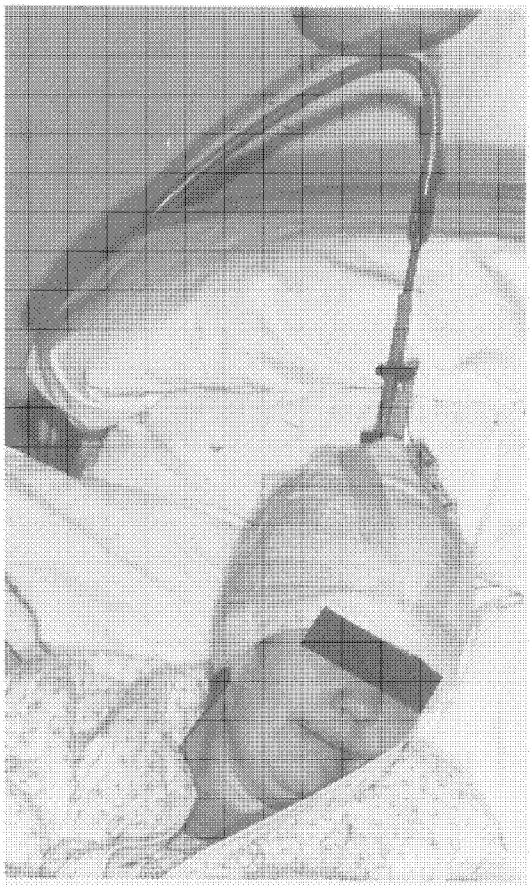

Fig. 4. A patient in bed attached to the machine while undergoing treatment.

a remote control unit at the door causing automatic source withdrawal when the room has to be entered.

At completion the balloon is deflated, the tube removed and the skin closed under local anaesthetic with strict asepsis. Patients seem to tolerate this procedure well and are usually discharged within a week.

DISCUSSION

Our approach is based on the belief that aggressive reduction in tumour volume offers the best form of palliation. Surgical debulking reduces the number of hypoxic cells and complements tumour bed irradiation as the next logical step. The technique of remotely controlled afterloading in brachytherapy is well established in other disciplines (Henschke *et al.*, 1964; Nori *et al.*, 1985; Mantell *et al.*, 1986; Hilaris *et al.*, 1987), but technical problems and availability of apparatus have limited its use in neurosurgery. It is advantageous as it not only eliminates radiation exposure to personnel, but allows flexibility of the treatment schedule and patient movements (Godden, 1988).

This method makes use of an advanced, purpose-built system which is readily available at radiotherapy centres. It could, therefore, be launched with the uncommon luxury of very limited additional expenditure and many of the initial problems associated with new approaches have been avoided.

Postimplantation adjustment of the radioactive sources becomes easy with the remote control and pneumatic transfer system of the Selectron machine and safe as it minimizes catheter manipulation. Migration of brachytherapy sources after implantation is a known problem in neurosurgery (Gutin and Dormandy, 1982) but this is largely overcome by microprocessor control in the Selectron system that guarantees constant accuracy of source positions to within 1mm.

Caesium-137, which emits both gamma and beta rays, was chosen because of the availability and convenience of the Selectron system. Its use is beneficial, however, since its long half-life of 30 years means a decay correction of only 2% per year while the unwanted beta rays can be absorbed by a relatively small thickness of stainless steel. A certain measure of dosimetrical versatility is possible in that the positions of the active beads can be changed to produce an isodose distribution specific to the geometry of the individual tumour beds.

We now deliver an absorbed dose of 50 Gy at 0.5 cm depth from the surface of the balloon. This is of the same order of magnitude as that used by others using stereotactically implanted sources (Gutin *et al.*, 1984) and takes into account the known tolerance of normal brain, the previously administered external beam radiotherapy and the remaining rim of tumour tissue. The dose at the surface of the balloon depends on the number and arrangement of sources as well as the balloon diameter and can be as high as 70 Gy.

The configuration of the balloon plays a key role in producing an acceptable dose distribution. The inverse square relationship between absorbed dose and distance from the source results in the larger the balloon diameter the greater the relative dose at prescribed distance from the balloon's surface. In practice it means that the balloon diameter should not be less than 2.5 cm in order to allow the depth dose at 0.5 cm from the surface to be greater than 50% of that at the surface. The balloon also acts as a buffer that absorbs the unacceptably high doses close to the sources and has a mechanical function in that it anchors the tube and acts as a stabilizer.

This system has been designed to irradiate the tumour bed locally. If therapeutic efficacy is shown in cases of relapse, the technique may then be used in primary therapy to give a high tumour-bed dose in association with external beam radiotherapy.

Interstitial irradiation with long-term implants has been used in glioma, but a major problem has been the high incidence of late radionecrosis necessitating further surgical intervention to decrease intracranial pressure (Gutin and Dormandy, 1982; Saleman *et al.*, 1986). This problem will be avoided by a removable catheter system such as ours, which is implanted into an already debulked tumour.

Patients seem to tolerate the procedure well. The introduction of infection remains a theoretical hazard, but removal of the applicator within 48 hours and appropriate antibiotic cover should reduce infective complications to a minimum. The size of the applicator makes it impractical to treat deep-seated gliomas in this way and as such represents its major limitation. There are other machines available, however, which use different sized applications which may enable this problem to be overcome in future.

We are evaluating this method on a prospective basis and the preliminary results will be reported elsewhere.

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References

Godden TJ (1988). In *Physical Aspects of Brachytherapy*. Adam Hilger, Bristol, pp.212–214.

Gutin PH, Dormandy RH (1982). A coaxial catheter system for

afterloading radioactive sources for the interstitial irradiation of brain tumours. Technical note. *Journal of Neurosurgery*, **56**, 734–735.

Gutin PH, Phillips TL, Wara WM, Leibel SA, Hosobuchi Y, Levin VA, *et al.* (1984). Brachytherapy of recurrent malignant brain tumours with removable high activity iodine-125 sources. *Journal of Neurosurgery*, **60**, 61–68.

Gutin PH, Leibel SA, Wara WM, Choucair A, Levin VA, Phillips TL *et al.* (1987). Recurrent malignant gliomas: survival following interstitial brachytherapy with high-activity Iodine-125 sources. *Journal of Neurosurgery*, **67**, 864–873.

Henschke UK, Hilaris BS, Mahan GD (1964). Remote afterloading with intracavitary applicators. *Radiology*, **83**, 344–345.

Hilaris BS, Nori D, Anderson LL (1987). New approaches to brachytherapy. *Important Advances in Oncology*, 237–261.

Hochberg HF, Pruitt A (1980). Assumptions in the radiotherapy of glioblastoma. *Neurology*, **30**, 907–911.

Leibel SA, Sheline GE (1987). Tolerance of the central and peripheral nervous system to therapeutic irradiation. In *Advances in Radiation Biology*, eds Lett JT, Altmann KI, pp.257–258. Academic Press, New York.

Mantell BS, Klevenhagen SC, Afshar F (1986). An afterloaded applicator for the interstitial irradiation of brain tumours. *Clinical Radiology*, **37**, 35–38.

Murray KJ, Blumberg A. Strubler K, Sirota R, Altman J (1986). Permanent radioactive iodine seed implants following radical resection in recurrent human malignant astrocytomas. In *Biology of Brain Tumour*, eds Walker MD, Thomas DGT, pp.355–363. Martinus Nijhoff, Boston.

Nelson DF, Urtasun RC, Saunders WM, Gutin PH, Sheline GE (1986). Recent and current investigations of radiation therapy of malignant gliomas. *Seminars in Onchology*, **13**, 46–55.

Nori D, Hilaris BS, Chada M, Bains M, Jain S, Hopfan S *et al.* (1985). Clinical applications of a remote afterloader. *Endocurietherapy Hyperthermia and Oncology*, **1**, 193–200.

Roberts DW, Coughlin CT, Wong, TZ, Fratkin JD, Douple EB, Strohben JW (1986). Interstitial hyperthermia and brachytherapy in treatment of malignant glioma. A phase 1 clinical trial. *Journal of Neurosurgery*, **64**, 581–587.

Salcman M (1980). Survival in glioblastoma: historical perspective. *Neurosurgery*, **7**, 435–439.

Salcman M, Sewchand W, Amin PP, Bellis EH (1986). Technique and preliminary results of interstitial irradiation for primary brain tumours. *Journal of Neuro-oncology*, **4**, 141–149.

Sewchand W, Amin PP, Dryzmala RE, Salazar OM, Salcman M, Samaras GM *et al.* (1984). Removable high-intensity Iridium-192 brain implants. Technique and in vivo measurements in canine brain, *Journal of Neuro-oncology*, **2**, 177–185.

Walker MD, Strike TA, Sheline GE (1979). An analysis of dose-effect relationship in the radiotherapy of malignant gliomas. *International Journal of Radiation Oncology, Biology, Physics*, **5**, 1725–1731.

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Exhibit 6

US006482142B1

(12) **United States Patent**
Winkler et al.

(10) **Patent No.: US 6,482,142 B1**
(45) **Date of Patent: Nov. 19, 2002**

(54) **ASYMMETRIC RADIATION DOSING APPARATUS AND METHOD**

(75) Inventors: **Rance A. Winkler**, Atlanta; **Timothy J. Patrick**, Alpharetta, both of GA (US)

(73) Assignee: **Proxima Therapeutics, Inc.**, Alpharetta, GA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/464,727**

(22) Filed: **Dec. 16, 1999**

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/293,524, filed on Apr. 15, 1999, which is a continuation-in-part of application No. 08/900,021, filed on Jul. 24, 1997, now Pat. No. 5,913,813.

(51) **Int. Cl.**[7] **A61N 5/00**
(52) **U.S. Cl.** **600/3**
(58) **Field of Search** 600/1–8

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,706,652	A	11/1987	Horowitz	128/1.2
4,754,745	A	7/1988	Horowitz	128/1.2
5,422,926	A	6/1995	Smith et al.	378/121
5,562,594	A	10/1996	Weeks	600/3
5,724,400	A	3/1998	Swerdloff et al.	378/65
5,800,333	A	9/1998	Liprie	600/3
5,803,895	A	9/1998	Kronholz et al.	600/3
5,851,182	A	12/1998	Sahadevan	600/407
5,863,284	A	1/1999	Klein	600/3

FOREIGN PATENT DOCUMENTS

WO	WO 97/19723	6/1997	A61N/5/00

OTHER PUBLICATIONS

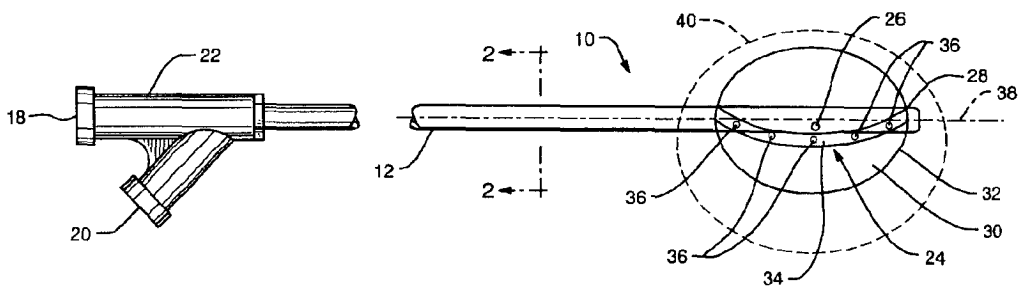
Ravinder, Nath, Ph.D. et al., Development of an ^{241} Am Applicator For Intracavitary Irradiation of Gynecologic Cancers, I.J. Radiation Oncology, Biology, Physics, May 1988, vol. 14, No. 5, pp. 969–978.

Primary Examiner—John P. Lacyk
(74) *Attorney, Agent, or Firm*—Thomas J. Engellenner; Ronald E. Cahill; Nutter McClennen & Fish LLP

(57) **ABSTRACT**

An interstitial brachytherapy apparatus of the invention delivers radioactive emissions in an asymmetric fashion to target tissue surrounding a surgical extraction site. The apparatus includes an expandable outer surface element defining an apparatus spatial volume, a radiation source disposed within the apparatus volume, and a means for providing predetermined asymmetric isodose curves within the target tissue. In one configuration, asymmetric isodose curves are created in the target tissue by shaping or locating the radiation source so as to be asymmetrically placed with respect to a longitudinal axis of the apparatus. In other configurations, asymmetric radiopaque shielding is provided between the radiation source and the target tissue. A surgical procedure using the apparatus is also described.

14 Claims, 4 Drawing Sheets



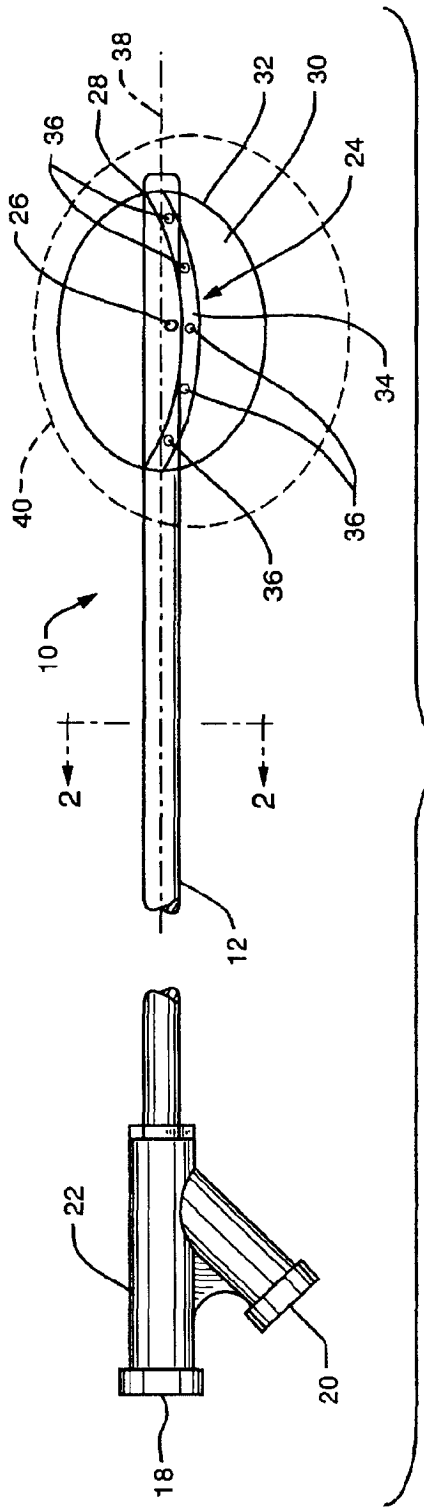


FIG. 1

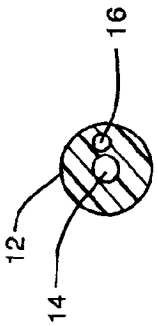


FIG. 2

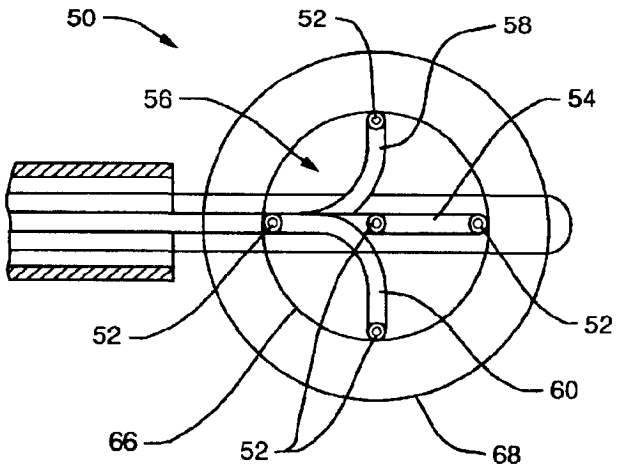


FIG. 3

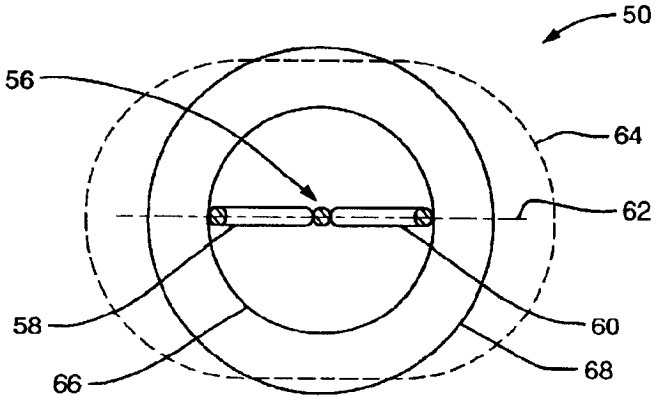


FIG. 3A

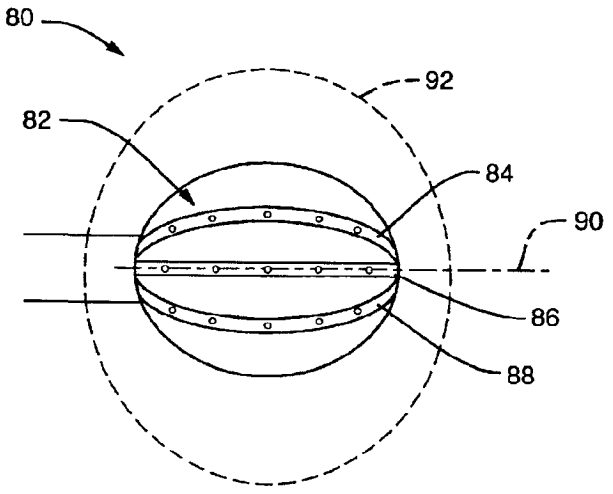


FIG. 4

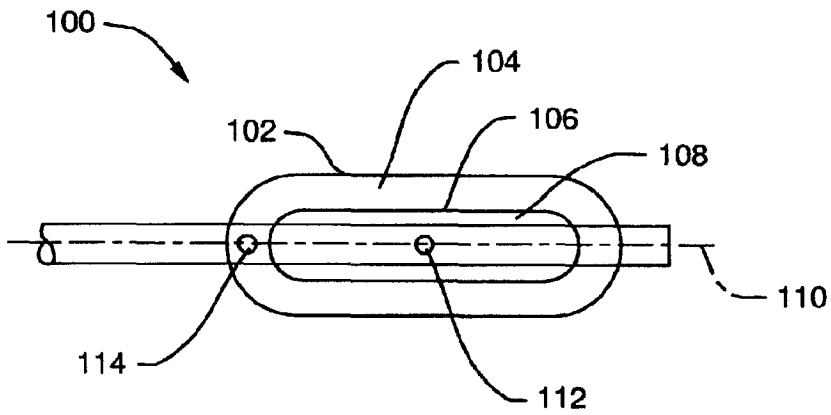

100
104
102
106
108
110
114
112

FIG. 5

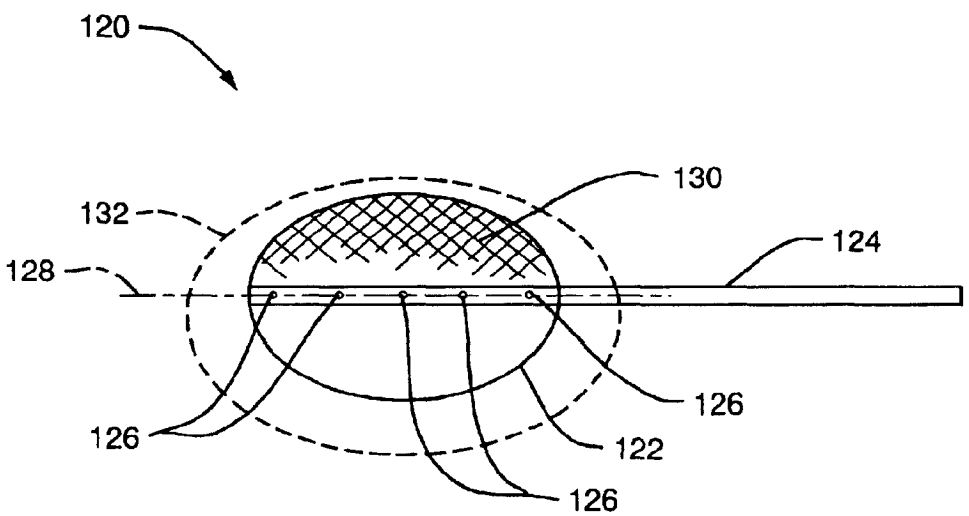

120
130
132
124
128
126
126
122
126

FIG. 6

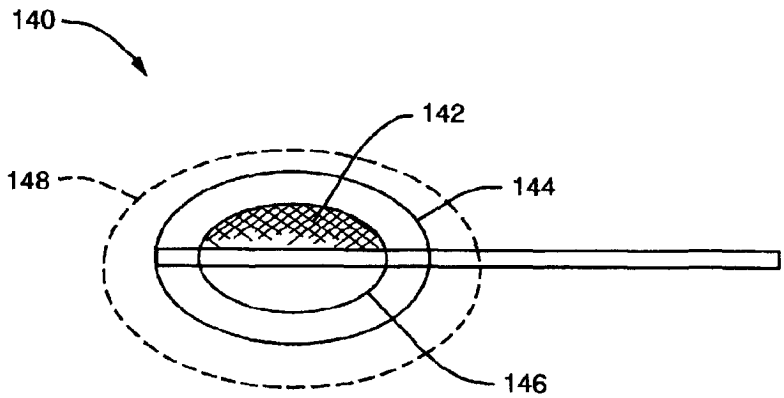


FIG. 7

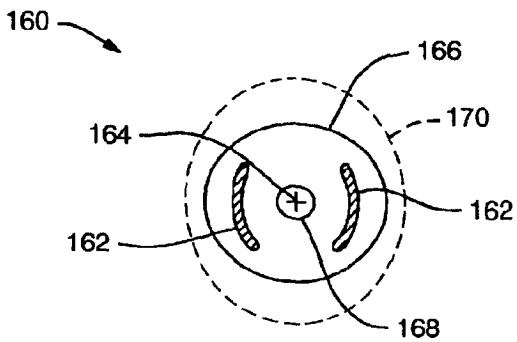


FIG. 8

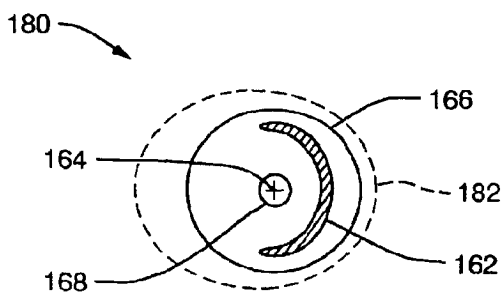


FIG. 9

ASYMMETRIC RADIATION DOSING APPARATUS AND METHOD

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of co-pending U.S. patent application Ser. No. 09/293,524, filed Apr. 15, 1999, pending which is a continuation-in-part U.S. patent application Ser. No. 08/900,021, filed Jul. 24, 1997 (now issued as U.S. Pat. No. 5,913,813 to Williams et al.); the contents of these applications are specifically incorporated herein by reference.

BACKGROUND OF THE INVENTION

The, invention relates generally to an apparatus for use in treating proliferative tissue disorders, and more particularly to an apparatus for the treatment of such disorders in the body by the application of radiation.

Malignant tumors are often treated by surgical resection of the tumor to remove as much of the tumor as possible. Infiltration of the tumor cells into normal tissue surrounding the tumor, however, can limit the therapeutic value of surgical resection because the, infiltration can be difficult or impossible to treat surgically. Radiation therapy can be used to supplement surgical resection by targeting the residual tumor margin after resection, with the goal of reducing its size or stabilizing it. Radiation therapy can be administered through one of several methods, or a combination of methods, including external-beam radiation, stereotactic radiosurgery, and permanent or temporary interstitial brachytherapy. The term "brachytherapy," as used herein, refers to radiation therapy delivered by a spatially confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site. Owing to the proximity of the radiation source, brachytherapy offers the advantage of delivering a more localized dose to the target tissue region.

For example, brachytherapy is performed by implanting radiation sources directly into the tissue to be treated. Brachytherapy is most appropriate where 1) malignant tumor regrowth occurs locally, within 2 or 3 cm of the original boundary of the primary tumor site; 2) radiation therapy is a proven treatment for controlling the growth of the malignant tumor; and 3) there is a radiation dose-response relationship for the malignant tumor, but the dose that can be given safely with conventional external beam radiotherapy is limited by the tolerance or normal tissue. In brachytherapy, radiation doses are highest in close proximity to the radiotherapeutic source, providing a high tumor dose while sparing surrounding normal tissue. Interstitial brachytherapy is useful for treating malignant brain and breast tumors, among others.

Interstitial brachytherapy is traditionally carried out using radioactive seeds such as ^{125}I seeds. These seeds, however, produce inhomogeneous dose distributions. In order to achieve a minimum prescribed dosage throughout a target region of tissue, high activity seeds must be used, resulting in very high doses being delivered in some regions in proximity to the seed or seeds which can cause radionecrosis in healthy tissue. One attempt to address this problem, at least with respect to limiting dosages to critical organs near the radioactive seed site, has been to provide a shield directly on a portion of the seed or on an applicator that holds the seed to shield the particularly sensitive tissue. (E.g., Nath et al., Development of an ^{241}Am Applicator for Intracavitary Irradiation of Gynecologic Cancers, *Intl. J. Radiation Oncology Biol. Phys.*, Vol., 14, pp. 969–978.) While this approach may be appropriate for some applications, it may still be overly "hot" for treating proximate tissue on the unshielded side of the seed, while not providing an effective dose on the shielded side of the seed.

Williams U.S. Pat. No. 5,429,582, entitled "Tumor Treatment," describes a method and apparatus for treating tissue surrounding a surgically excised tumor with radioactive emissions to kill any cancer cells that may be present in the tissue surrounding the excised tumor. In order to implement the radioactive emissions, Williams provides a catheter having an inflatable balloon at its distal end that defines a distensible reservoir. Following surgical removal of a tumor, the surgeon introduces the balloon catheter into the surgically created pocket left following removal of the tumor. The balloon is then inflated by injecting a fluid having one or more radionuclides into the distensible reservoir via a lumen in the catheter.

The apparatus described in Williams solves some of the problems found when using radioactive seeds for interstitial brachytherapy, but leaves some problems unresolved. The absorbed dose rate at a target point exterior to a radioactive source is inversely proportional to the square of the distance between the radiation source and the target point. s a result, where the radioactive source has sufficient activity to deliver a prescribed dose, say 2 centimeters into the target tissue, the tissue directly adjacent the wall of the distensible reservoir, where the distance to the radioactive source is very small, may still be overly "hot" to the point where healthy tissue necrosis may result. In general, the amount of radiation desired by the physician is a certain minimum amount that is delivered to a region up to about two centimeters away from the wall of the excised tumor. It is desirable to keep the radiation that is delivered to the tissue in the target treatment region within a narrow absorbed dose range to prevent over-exposure to tissue at or near the reservoir wall, while still delivering the minimum prescribed dose at the maximum prescribed distance from the reservoir wall. It is also desirable, at least in some applications, to provide these advantages while tailoring the radiation dosage to avoid fully dosing sensitive tissue or to reduce the amount of radiation that escapes the patient's body.

There its still a need for an instrument which can be used to deliver radiation from a radioactive source to target tissue within the human body with a desired intensity and at a predetermined distance from the radiation source without over-exposure of body tissues disposed between the radiation source and the target, and with the ability to shape the radiation dose to protect sensitive tissue or to protect against radiation exposure outside of the patient's body which may affect healthcare providers or others who might come close to the patient.

SUMMARY OF THE INVENTION

The present invention solves the problems described above by providing an interstitial brachytherapy apparatus for delivering radioactive emissions in an asymmnetric fashion to target tissue surrounding a surgical extraction site. The apparatus includes an expandable outer surface element defining an apparatus spatial volume, a radiation source disposed within the apparatus volume, and a means for providing predetermined asymmnetric isodose profile within the target tissue.

In one configuration, asymmetric isodose curves are created in the target tissue by shaping or locating the radiation source so as to be asymmetrically placed with respect to a

longitudinal axis of the apparatus. In one example of an apparatus having this configuration, an inner volume containing a liquid radioisotope is asymmetrically placed within the apparatus volume so as to result in an isodose profile in the target tissue that is asymmetric about the longitudinal axis of the apparatus.

In another example, the radiation source comprises a plurality of spaced apart solid radioactive particles disposed within the apparatus volume and arranged to provide a predetermined asymmetric isodose curve within the target tissue. In one particular example, the plurality of spaced apart radioactive particles are provided on a single elongate member that is shaped so that some of the radioactive particles are farther from the longitudinal axis of the apparatus than others. In other particular examples, a plurality of members carrying radioactive particles are provided with at least one of the members being shaped so as to place at least one radioactive particle asymmetrically with respect to the longitudinal axis of the apparatus.

An interstitial brachytherapy apparatus of the invention may also be implemented in a device having an expandable outer surface defining an apparatus volume, a radiation source disposed within and spaced apart from the expandable outer surface, and at least one asymmnetric radiation shield spaced apart from the radiation source, the asymmetric radiation shielding resulting in predetermined asymmetric isodose curves with in the target tissue. In one embodiment, radiopaque shielding is provided on a portion of the expandable outer surface. In another embodiment, the radiation source is encompassed within a second, inner surface within the apparatus volume, with radiopaque shielding provided on at least a portion of the inner surface. In still further embodiments, one or more radiation shields are spaced apart from the radiation source and within the apparatus volume to achieve the desired asymmetric isodose distribution within the target tissue.

The invention also provides a method for treating a proliferating tissue disease using interstitial brachytherapy at an internal body location. The method includes surgically creating access to the proliferating tissue within a patient and surgically resecting at least a portion of the proliferating tissue to create a resection cavity within body tissue. An interstitial brachytherapy apparatus for delivering radioactive emissions as described above is then provided and intra-operatively placed into the resection cavity. After a prescribed absorbed dose has been delivered to tissue surrounding the apparatus, the apparatus is removed. The radioactive source material may be placed into the interstitial brachytherapy apparatus after the apparatus is placed in the resection cavity, and may be removed before the apparatus is removed. The method has particular applications to brain and breast cancers.

DESCRIPTION OF THE DRAWINGS

The foregoing features, objects and advantages of the invention will become apparent to those skilled in the art from the following detailed description of a preferred embodiment, especially when considered in conjunction with the accompanying drawings in which:

FIG. **1** is a side view of an interstitial brachytherapy apparatus of the invention for delivering asymmetric radioactive doses to body tissue;

FIG. **2** is a cross-sectional view taken along the line 2—2 in FIG. 1;

FIG. **3** is a side view of an additional embodiment of an interstitial brachytherapy apparatus of the invention;

FIG. **3A** is an end view of the interstitial brachytherapy apparatus of FIG. **3**;

FIG. **4** is a side view of an additional embodiment of an interstitial brachytherapy apparatus of the invention;

FIG. **5** is a side view of an interstitial brachytherapy apparatus of the invention configured for use with a liquid radiation source.

FIG. **6** is a side view of an interstitial brachytherapy device of the invention employing radiopaque coatings;

FIG. **7** is a side view of an interstitial brachytherapy device of the invention employing radiopaque coating and a liquid radiation source; and

FIGS. **8** and **9** are end views of interstitial brachytherapy devices of the invention employing radiopaque shields.

DESCRIPTION OF THE PREFERRED EMBODIMENT

A surgical instrument **10** for providing radiation treatment to proliferative tissue in a living patient is illustrated in FIG. **1**. Surgical instrument **10** includes a tubular body member **12** having first and second lumens **14** and **16** (FIG. **2**) extending from proximal ports **18** and **20** in a molded hub **22**. The first lumen **14** carries a radioactive source **24** and second lumen **16** communicates with inflation port **26** formed through the side wall of the tube **12**.

Affixed to the tubular body **12** proximate the distal end **28** thereof is an outer spatial volume **30** defined by an outer polymeric film barrier **32** that is appropriately spaced from the radioactive source **24**. Outer volume **30** encompasses inflation port **26**. With no limitation intended, the distensible polymeric film walls may comprise a biocompatible, radiation resistant polymer, such as silastic rubbers, polyurethanes, polyethylene, polypropylene, polyester, or PVC. The outer spatial volume **30** may be filled with air, saline or, alternatively, a radiation absorbing fluid, such as a contrast media used in angiography. Alternatively, the surface of outer volume **30** need not be a solid material. For example the surface of the outer volume **30** could be an expandable cage formed from a shape memory metal, such as nitinol, or a suitable plastic, such as an expandable polyethylene cage. Such a cage can be formed in the desired shape to conform to a particular isodose profile, contracted for delivery to the target site in vivo, then expanded to cause the tissue surrounding the surgically resected region to take the appropriate shape. The size of the outer spatial volume **30** generally will correspond approximately to the amount of tissue resected. For some applications, the size of the outer spatial volume **30** may be slightly smaller than the resected volume while for other applications, the outer spatial volume will be slightly larger than the resected volume, allowing the expandable surface of the outer spatial volume to urge tissue on the surface of the resected region into the appropriate shape to promote an even dose distribution around the outer spatial volume in the target tissue. In typical applications, the outer spatial volume has a diameter of approximately 2 to 6 centimeters.

Radiation source **24** comprises a wire **34** having one or more solid radioactive particles **36** located on the wire **34**. For example, radioactive micro spheres of the type available from the 3M Company of St. Paul, Minn., may be used as the solid radioactive particles. Such a solid radioactive particle configuration offers an advantage in that it allows a wider range of radionuclides than if one is limited to liquids. Solid radionuclides that could be used with the delivery device of the present invention are currently generally available as brachytherapy radiation sources. Examples of

radioactive materials which can be selected by a person of ordinary skills in the art for use with the present invention may be found in Tables 1 to 4 of PCT Publication WO 97/19723, which is hereby incorporated by reference.

The, radioactive source **24** can either be preloaded into the catheter at the time of manufacture, or loaded into the device after it has been implanted into the space formerly occupied by the excised tumor. If loaded after implantation, the solid radiation emitting material **36** can be inserted through lumen **14** on a wire **34**, for example using an afterloader (not shown).

Radiation source **24** has an asymmetric configuration with respect to a longitudinal axis **38** of the instrument **10**. That is, radiation source **24** is shaped so as to result in an isodose profile **40** that varies radially about the longitudinal axis **38**. More simply, the isodose profile **40** of FIG. **1** has a shorter radius from the longitudinal axis **38** on the top side of the instrument **10** as shown in FIG. **1** than on the bottom side. The asymmetrically shaped isodose curve **40** may be created by providing a plurality of solid radioactive particles **36** on a curved wire **34** in a spaced apart relationship. This configuration will result in certain of the solid radioactive particles **36** being farther from the longitudinal axis **38** of the instrument **10** than others, and will result in the illustrated asymmetric isodose profile **40**. One way to provide the illustrated radioactive source **24** configuration is to form wire **34** from a solid or tubular shape memory alloy such as nickel-titanium alloys known in the art to have such properties. Wire **34** can then be preformed to the desired shape, can be compressed into a substantially straight configuration to pass through lumen **14**, and will resume its desired shape once inside volume **30** where wire **34** will be free from steric constraints imposed inside the lumen **14**. The resulting asymmetric isodose curve **40** can be further tailored by using solid radioactive particles **36** having differing specific activities to achieve the desired dosing.

In,one embodiment, volume **30** and barrier **32** act to separate target tissue from the radiation source **24**. Ideally, radiation therapy should make use the inherent difference in radiosensitivity between the tumor and the adjacent normal tissues to destroy cancerous tissue while causing minimal disruption to surrounding normal tissues. At high doses of radiation, however, the percentage of exposed cells that survive treatment decreases with first-order kinetics in proportion to increasing radiation dose. With increasing cell death comes increasing risk of necrosis or tissue death in healthy tissue that is treated with a high dose of radiation. Accordingly, it is desirable to keep the maximum radiation dose delivered by the brachytherapy apparatus as low as possible while still delivering the desired therapeutic dose to the desired range of tissue. One method for achieving this result is to provide a "hotter" radiation source in a spaced apart relationship to the target tissue. In this way, because the intensity of the radiation emitted by a source drops with the square of the distance from the source, the effective dosage may be maintained below necrosis levels in target tissue closest to the interstitial brachytherapy apparatus while providing the required dosage to a greater depth into the target tissue. (See, e.g., U.S. Pat. No. 5,913,813 which is hereby incorporated by reference in its entirety.) The capability of the apparatus of the invention to deliver absorbed doses deeper into the target tissue than prior interstitial brachytherapy devices while controlling the dose in proximity to the apparatus to reduce or eliminate the risk of healthy tissue necrosis allows for the use of brachytherapy in a greater number of cases.

For example, it is desirable to provide an interstitial brachytherapy device configured to provide a dose in a therapeutic range, say between 40 to 60 Gray, at a distance between 0.5 and 1.0 cm from the outer spatial volume for an outer spatial volume having a diameter of 4.0 cm and being in contact with the resection cavity wall. In a typical embodiment, the radioactive source material ranges from approximately 150 to 450 mCi in activity and encompasses most of the target treatment area with a 0.4 to 0.6 Gray/hour isodose contour. At this treatment rate, treatment may be completed in approximately 3 to 7 days, or more commonly, in approximately 3 to 5 days.

In some applications, the desired dosing profile is consistent with the shape of the outer volume **30**. That is, the absorbed dose within the target tissue at points equidistant from the surface **32** of the outer spatial volume **30** should be substantially uniform in substantially every direction. Put another way, the three dimensional isodose profiles generated by the radiation source should be substantially similar in shape to the outer spatial volume **30**. Where the apparatus of the invention is deployed in soft tissue, it may also be important for the surface **32** of the outer spatial volume **30** to be sufficiently firm so as to force the target tissue to take on the shape of the surface **30** so that the desired relationship between the isodose profiles and the target tissue is achieved

While the interstitial brachytherapy device **10** of FIG. **1** may employ these techniques to positive effect, this device specifically alters the isodose profile for applications where particularly sensitive tissue or other concerns result in a desire to limit the dosage on one or more sides of the device as illustrated by isodose curve **40**.

In a further embodiment of the brachytherapy device **50** of the invention, illustrated in FIG. **3**, three solid radiation particles **52** are provided in a linear portion **54** of radiation source **56**, while two additional radiation particles **52** are provided on co-planar extending portions **58**, **60** of radiation source **56**. An end view of the device **50** of FIG. **3** is shown in FIG. 3A with extending portions **58**, **60** provided in a single plane **62**, and resulting in isodose profile **64**. A second inner, expandable surface **66** can also be provided within outer surface **68**; the inner surface **66** enclosing the entirety of radiation source **56**.

By providing extending portions **58**, **60** having radioactive particles in the indicated co-planar relationship, areas of reduced dosage can be created on opposed sides of the device while maintaining symmetric dosing in all other directions. Of course, the number of sources and their configuration can be changed to create a desired asymmetric dosage. For example, an additional source could be added, for example above plane **62**, to result in a symmetric isodose profile in all directions except the direction below the plane **62** which would have a lower dosage.

An additional device **80** of the invention, shown in FIG. **4**, includes a radiation source **82** that is made up of three wires **84**, **86**, **88**, each having a plurality of solid radiation particles. Wire **86** is a straight wire extending along the longitudinal axis **90** of the device, while wires **84**, **88** each curve as wire **34** described above with respect to FIG. **1**. Wires **84**, **88** are coplanar, resulting in an isodose profile **92** that is similar to isodose profile **64** of FIG. 3A. That is, the isodose profile will be symmetric in the plane in which the wires **84**, **88** are disposed, but will have areas of reduced dosage in directions transverse to that plane (i.e., in FIG. **4**, in the directions into and out of the page). As with the device **50** of FIGS. **3** and 3A, device **80** can be configured with more or fewer wires **84**, **86**, **88**, and can be provided in configurations other than the depicted co-planar configuration in order to achieve desired asymmetric isodose profiles.

The asymmetric dosing effect achieved by the devices described above can also be achieved using a liquid radiation source. For example, device **100**, illustrated in FIG. **5**, has an outer surface **102** defining an outer volume **104** and an inner surface **106** defining an inner volume **108**. The inner surface **106** is asymmetrically shaped or located with respect to the longitudinal axis **110** of the device **100** so as to result in the desired asymmetric dosing when the inner volume **108** is filled with a radioactive fluid. The inner volume **108** is spaced apart from the outer surface **102** and can be filled with a material containing a predetermined radionuclide, for example, I-125, I-131, Yb-169 or other source of radiation, such as radionuclides that emit photons, beta particles, gamma radiation, or other therapeutic rays. The radioactive material contained within the inner volume **108** can be a fluid made from any solution of radionuclide(s), e.g., a solution of Ir-192, I-125 or I-131. A radioactive fluid can also be produced using a slurry of a suitable fluid containing small particles of solid radionuclides, such as Au-198, Y-90. Moreover, the radionuclide(s) can be embodied in a gel. One radioactive material useful in the invention is Iotrex™, a sterile single use, non-pyrogenic solution containing sodium 3-(^{125}I)iodo-4-hydroxybenzenesulfonate (^{125}I-HIBS), available from Proxima Therapeutics, Inc. of Alpharetta, Ga. The inner volume **108** may be filled with radioactive fluid through port **112**. Similarly, outer volume **104** can be filled on inflated using port **114**.

A desired asymmetric dosing profile having the dosing characteristics described above may also be created by using asymmetric shielding between the radiation source and the target tissue as illustrated in FIGS. **6** through **9**. In the device **120** of FIG. **6**, a balloon **122** is located on the distal end of catheter **124**. Radioactive particles **126** are disposed along the longitudinal axis **128** of the device. A portion of the surface, either inner or outer, of balloon **122** is coated with a radiopaque material **130** to result in asymmetric isodose curve **132**. Radiopaque materials suitable for coating onto a polymeric surface of balloon **122** include, for example, barium, tungsten, bismuth, tantalum and tin.

A further device **140** having radiopaque shielding **142** is illustrated in FIG. **7**. Device **140** includes an outer volume surface **144** and an inner volume surface **146**. Inner surface **146** may contain a liquid radiation source, or may enclose one or more solid particles as used in device **120** (FIG. **6**). In device **140**, the radiopaque material **142** is coated onto a portion of either the inner or outer side of the inner volume surface **146**, resulting in a desired asymmetric isodose profile **148**.

Additional devices **160**, **180** of the invention having radiation shielding **162** are illustrated in FIGS. **8** and **9**, respectively. In these devices **160**, **180**, one or more radiation shields **162** are provided between and spaced apart from a radiation source (not shown) located along a longitudinal axis **164** of the device and the target tissue, which will be located outside of expandable surface **166**. The radiation source can include a liquid or a solid radiation source as described above. Shields **162** can be formed from radiopaque materials including those described above with respect to the radiopaque coating and can extend longitudinally from a base on the device located within the expandable surface **166**.

As shown in FIG. **8**, device **160** has two radiation shields **162** on opposed sides of catheter **168**. This configuration results in lower radiation dosing on the two sides of the device **160** on which the shields **162** are located as shown by isodose curve **170**. Device **180** (FIG. **9**) has a single radiation shield **162** resulting in an asymmetric isodose curve **182** as shown. A person or ordinary skill in the art will recognize that other configurations may be employed to achieve desired isodose curves.

The interstitial brachytherapy apparatus of the invention can be used in the treatment of a variety of malignant tumors, and is especially useful for in the treatment of brain and breast tumors.

Many breast cancer patients are candidates for breast conservation surgery, also known as lumpectomy, a procedure that is generally performed on early stage, smaller tumors. Breast conservation surgery is typically followed by postoperative radiation therapy Studies report that 80% of breast cancer recurrences after conservation surgery occur near the original tumor site, strongly suggesting that a tumor bed "boost" of local radiation to administer a strong direct dose may be effective in killing any remaining cancer and preventing recurrence at the original site. The apparatus described herein can be used for either the primary or boost therapy. Numerous studies and clinical trials have established equivalence of survival for appropriate patients treated with conservation surgery plus radiation therapy compared to mastectomy.

Surgery and radiation therapy are also the standard treatments for malignant solid brain tumors. The goal of surgery is to remove as much of the tumor as possible without damaging vital brain tissue. The ability to remove the entire malignant tumor is limited by its tendency to infiltrate adjacent normal tissue. Partial removal reduces the amount of tumor to be treated by radiation therapy and, under some circumstances, helps to relieve symptoms by reducing pressure on the brain.

A method according to the invention for treating these and other malignancies begins by surgical resection of a tumor site to remove at least a portion of the cancerous tumor and create a resection cavity. Following tumor resection, but prior to closing the surgical site, the surgeon intraoperatively places an interstitial brachytherapy catheter apparatus, having an inner spatial volume and an outer spatial volume as described above but without having the radioactive source material loaded, into the tumor resection cavity. Once the patient has sufficiently recovered from the surgery, the interstitial brachytherapy catheter is loaded with a radiation source. The radioactive source dwells in the catheter until the prescribed dose of radiotherapy is delivered, typically for approximately a week or less. The radiation source is then retrieved and the catheter is removed. The radiation treatment may end upon removal of the brachytherapy apparatus, or the brachytherapy may be supplemented by further doses of radiation supplied externally.

It will be understood that the foregoing is only illustrative of the principles of the invention, and that various modifications can be made by those skilled in the art without departing from the scope and spirit of the invention, including, but not limited to, combinations of elements from different embodiments found herein. All references cited herein are expressly incorporated by reference in their entirety.

What is claimed is:

1. An interstitial brachytherapy apparatus for treating target tissue surrounding a surgical extraction comprising:

an expandable outer surface defining a three-dimensional apparatus volume configured to fill an interstitial void created by the surgical extraction of diseased tissue and define an inner boundary of the target tissue being treated;

a radiation source disposed completely within the expandable outer surface and located so as to be spaced apart from the apparatus volume, the radiation source further being asymmetrically located and arranged within the expandable surface to provide predetermined asymmetric isodose curves with respect to the apparatus volume.

2. A surgical apparatus for providing radiation treatment to target tissue comprising:

an expandable outer surface defining an apparatus volume;

a radiation source replaceably disposable within the expandable outer surface, the radiation source comprising a plurality of solid radiation sources arranged to provide predetermined asymmetric isodose curves within the target tissue, the plurality of solid radiation sources being provided in a spaced apart relationship on a single elongate member, the single elongate member being shaped to provide asymmetric placement of the spaced apart solid radiation sources with respect to a longitudinal axis through the apparatus volume.

3. The apparatus of claim **2**, further comprising a catheter in communication with the apparatus volume, the elongate member extending through the catheter into the apparatus volume.

4. The apparatus of claim **3**, wherein the elongate member is formed of a shape memory alloy, the elongate member being shaped to provide asymmetric placement of the spaced apart solid radiation sources, taking on a substantially straight shape while being inserted through the catheter to the apparatus volume, and resuming an asymmetric shape when extended into the apparatus volume.

5. A surgical apparatus for providing radiation treatment to target tissue comprising:

an expandable outer surface defining an apparatus volume;

a radiation source replaceably disposable within the expandable outer surface, the radiation source comprising a plurality of solid radiation sources arranged to provide predetermined asymmetric isodose curves within the target tissue, wherein at least one of the plurality of solid radiation sources has a different specific activity from at least one other solid radiation source.

6. A surgical apparatus for providing radiation treatment to target tissue comprising:

an expandable outer surface defining an apparatus volume;

a radiation source replaceably disposable within the expandable outer surface, the radiation source comprising a plurality of solid radiation sources arranged to provide predetermined asymmetric isodose curves within the target tissue, the plurality of radiation sources being provided on at least two elongate members extending into the apparatus volume, at least one of the elongate members being shaped to provide asymmetric placement of a radiation source with respect to a longitudinal axis through the apparatus volume.

7. The apparatus of claim **6**, wherein each of the at least two elongate members includes a plurality of solid radiation sources provided in a spaced apart relationship.

8. The apparatus of claim **1**, wherein the expandable outer surface is sufficiently rigid to deform the target tissue into the shape of the expandable outer surface, causing the predetermined asymmetric isodose curves to penetrate into the target tissue to a prescribed depth.

9. An interstitial brachytherapy apparatus for treating target tissue surrounding a surgical extraction comprising:

an expandable outer surface having a base and defining a three-dimensional apparatus volume configured to fill an interstitial void created by the surgical extraction of diseased tissue and define an inner boundary of the target tissue being treated;

a radiation source disposed completely within and spaced apart from the expandable outer surface; and

an asymmetric radiation shield spaced apart from the radiation source, the asymmetric radiation shield providing predetermined asymmetric isodose curves with respect to the apparatus volume.

10. The apparatus of claim **9**, wherein the asymmetric radiation shield comprises a radio-opaque material disposed on only a portion of the expandable outer surface.

11. The apparatus of claim **10**, wherein the expandable outer surface comprises an inflatable balloon.

12. The apparatus of claim **11**, wherein the radiation shield comprises a barium material disposed a portion of the inflatable balloon.

13. The apparatus of claim **9**, further comprising at least one radiation shield extending from the base of the expandable outer surface toward an opposite end of the expandable surface, the shield being in between and spaced apart from the radiation source and the expandable outer surface, the shield forming a radio-opaque barrier between a portion of the radiation source and the target tissue.

14. The apparatus of claim **13**, wherein the radiation shield comprises two shields provided on opposite sides of the radiation source.

* * * * *

Exhibit 8

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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN JOSE DIVISION

XOFT, INC., Plaintiff, vs. CYTYC CORPORATION and PROXIMA THERAPEUTICS, INC., Defendants. AND RELATED COUNTERCLAIMS.	Case No. CV 05-05312 RMW **DEFENDANT AND COUNTERCLAIMANT CYTYC CORPORATION'S OPENING CLAIM CONSTRUCTION BRIEF (PAT. L.R. 4-5(a))** Tutorial and Markman Hearing Date: December 20, 2006 Time: To Be Set Room: Courtroom 6, 4th Floor Judge: Hon. Ronald M. Whyte

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STATUTES

Pursuant to the Agreed Scheduling Order,[1] Defendant and Counterclaimant Cytyc Corporation ("Cytyc") respectfully submits this Brief addressing the construction of disputed terms, phrases and clauses in the asserted claims of U.S. Patent Nos. 5,913,813 (the "'813 patent") and 6,413,204 (the "'204 patent") (attached hereto as Exhibits A and B to the Declaration of Henry C. Su, respectively). Cytyc currently asserts claims 1, 2, 3, 4, 8 and 12 of the '813 patent and claims 1, 2, 3, 4, 8, 16, 17, 18, 19, 20, 21, 23, 24, 25, 26, 30, 32, 34, 35 and 36 of the '204 patent against Plaintiff Xoft, Inc. ("Xoft").

PRELIMINARY STATEMENT

The differences in the parties' approaches to construing the disputed terms are stark. Cytyc's proposed constructions are straightforward, applying the plain meaning that would be apparent to one of ordinary skill in the art when the disputed terms are read in light of the specification, in accordance with the Federal Circuit's recent *en banc* decision in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc), *cert. denied,* 126 S. Ct. 1332 (2006). In contrast, Xoft insists on improperly injecting into its proposed constructions of the disputed terms limitations that are nowhere found in the claim language and are not supported by the specification, in contravention of Federal Circuit law. Xoft also repeatedly attempts to limit the claim terms to exemplary embodiments in the specification, which is also contrary to the law. In a few instances where the patent specifically defines a claim term, Xoft refuses to acknowledge that express definition, crafting instead its own definition from whole cloth. Finally, Xoft cannot hope to establish by clear and convincing evidence that certain claims terms are indefinite. The testimony of Cytyc's expert, Dr. Lynn J. Verhey, shows that one skilled in the art, reading the disputed terms in light of the specification, understands exactly what is being claimed. Xoft's strained interpretations of the disputed terms and its meritless allegations of indefiniteness should thus be rejected.

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[1] The Agreed Scheduling Order called for Cytyc to file its Opening Claim Construction Brief on November 6, 2006. On account of the fact that the Court was moving the date for the technology tutorial and claim construction hearing from December 6-7, 2006 to December 20, 2006, the parties filed on November 3, 2006 a joint stipulation and proposed order requesting that the Court enlarge the briefing schedule. On November 7, 2006, the Court declined to enlarge the briefing schedule (other than to set the due date for the reply brief on December 7, 2006) and held that "[h]aving at least the minimum time periods set forth in Civil L.R. 7 to consider the parties' arguments would be particularly useful to the court in a case such as this." In response to this order, Cytyc moved promptly to finalize and file its Opening Claim Construction Brief, which is still being submitted more than 35 days before the scheduled hearing date.

BACKGROUND

I. THE TECHNOLOGY

The patents-in-suit relate to the field of treating proliferative tissue diseases like cancer with radiation. Traditionally, a patient diagnosed with a cancerous tumor would have the tumor removed and then the region of body where the tumor was located would be exposed to an external radiation beam in an attempt to ensure that any remaining cancerous cells are destroyed. One of the major disadvantages of external beam radiation therapy is that it is difficult to target just the diseased area and avoid irradiating significant portions of healthy tissue. Accordingly, it is medically desirable to use various devices and instruments to position the radiation source as close as possible to the diseased site. This technique is known as brachytherapy. The root "brachy" comes from the Greek word for "short distance."

The patents-in-suit are directed specifically to a type of brachytherapy known as interstitial brachytherapy, in which the radiation source is introduced in close proximity to diseased cells that are within the interstices of a body tissue. This technique requires creating some sort of path through the tissue to the reach the targeted site, and it can be contrasted with brachytherapy in which the radiation source is merely inserted into a natural body cavity like the bladder (intracavitary), into a body lumen like the urethra (intraluminal), or on the surface of the body (surface brachytherapy). For example, as taught by the patents-in-suit, a radiation source is introduced through the opening and cavity created by the tumor resection so that it can treat the diseased cells within the interstices of the tissue at the margins of the tumor resection site.

According to the invention described and claimed in the patents-in-suit, the radiation source is introduced into the resection cavity using a catheter. An expandable or inflatable device, such as a cage or balloon, is used to shape the resection cavity so that the radiation dose absorbed by the diseased cells within the interstices of the tissue at the margins of the cavity is made more uniform. Three primary factors affect the amount of the absorbed dose: (1) distance of the tissue to be treated from the radiation source, (2) the presence of a radiation attenuating medium such as air or a saline solution, and (3) the use of radiation shielding.

The patents-in-suit use these factors, individually or in combination, to improve treatment by controlling the "radial absorbed dose profile" and the "three-dimensional isodose profile." The former involves controlling the absorbed dose as a function of radial distance from the radiation source to points within the targeted tissue; the latter involves conforming the shape of the targeted tissue to a virtual, three-dimensional surface defined by points receiving the same radiation dose. To control the radial absorbed dose profile, one may surround the radiation source with a radiation attenuating medium to minimize the ratio of the absorbed dose at the wall of the tumor cavity to the dose within the interstices of the target tissue. If the ratio is too high, then "hot spots" can occur at the wall of the cavity, which cause healthy tissue to necrose. Controlling the three-dimensional isodose profile involves shaping the resected tumor cavity and adjusting the position of the radiation source relative to the cavity to create a desired, virtual isodose surface on which all points receive substantially the same dose. These points will be coincident with points within the interstices of the tissue to be treated.

II. THE EXPERTS

Although Cytyc bases its proposed constructions on the intrinsic evidence, *i.e.*, the patents' claim language, specifications, and prosecution histories, Cytyc also proffers the testimony of Dr. Lynn J. Verhey to provide the perspective of one skilled in the relevant art. *Phillips*, 415 F.3d at 1313 (claims must be construed from the perspective of one skilled in the art). In this case, a person of ordinary skill in the art has a background in radiation oncology physics with a focus on brachytherapy. Such individuals would hold a M.S. degree in Physics or Engineering, with 3 or more years of clinical medical physics experience, or a Ph.D. in Physics or Engineering with 2 or more years of clinical experience. (*See* Exhibit D to the Declaration of Henry C. Su (Declaration of Lynn J. Verhey, Ph.D. ("Verhey Rep.")) at 4:6-18.)

Dr. Verhey is an expert in the field of radiation oncology, with decades of experience. He is currently a Full Professor and Vice-Chair in the Department of Radiation Oncology at University of California, San Francisco. Dr. Verhey earned a Ph.D. in Physics and, in 1975, took a position as Hospital Radiation Physicist at Massachusetts General Hospital (MGH) with a concurrent continuing position as Assistant Professor at the Harvard Medical School. In 1990, he became Chief of the Physics Division and Associate Professor in the Department of Radiation Oncology at UCSF. He has

taught courses in physics, radiation, and medical physics (including radiation oncology). He has conducted research on new methods of delivering radiation to cancer patients and has published over 100 technical papers in that field. Dr. Verhey is a certified Therapeutic Radiological Physicist by the American Board of Radiology and is a fellow in the American Association of Physics in Medicine and the American Society of Therapeutic Radiology and Oncology. In sum, he is a well-recognized and independent expert in methods of delivering radiation to cancer patients.

By contrast, Xoft's expert, Paul A. Lovoi, Ph.D., did not attach a curriculum vitae to his report and his credentials in the relevant field are not otherwise apparent. Moreover, Dr. Lovoi is not independent. He is one of the founders of Xoft and was an officer of Xoft until recently. He now consults for Xoft and has worked for the company during the last decade. His report indicates a Ph.D. in physics but does not list any specific experience in the field of radiation oncology, other than 9 years of purported experience in "medical use of sources of radiation." Xoft is Dr. Lovoi's company – he founded it, he ran it, and he has devoted a good part of his life to it. This Court should weigh his opinions accordingly.

APPLICABLE LAW

Sitting *en banc*, the Federal Circuit recently clarified its guiding principles for construction of patent claims. *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005). In *Phillips*, the court emphasized the "primary importance" of the language of the claims themselves:

> It is a "bedrock principle" of patent law that "the claims of a patent define the invention to which the patentee is entitled the right to exclude." . . . That principle has been recognized since at least 1836, when Congress first required that the specification include a portion in which the inventor "shall particularly specify and point out the part, improvement, or combination, which he claims as his own invention or discovery." . . . In the following years, the Supreme Court made clear that the claims are "of primary importance, in the effort to ascertain precisely what it is that is patented." . . . Because the patentee is required to "define precisely what his invention is," the Court explained, it is "unjust to the public, as well as an evasion of the law, to construe it in a manner different from the plain import of its terms." . . .

415 F.3d at 1312 (citations omitted). The Federal Circuit also reaffirmed the time-honored rule that claim terms are generally to be given their ordinary and customary meaning to those skilled in the art:

> We have frequently stated that the words of a claim "are generally given their ordinary and customary meaning." . . . We have made clear, moreover, that the ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective

> filing date of the patent application. . . . The inquiry into how a person of ordinary skill in the art understands a claim term provides an objective baseline from which to begin claim interpretation.

Id. at 1312-13 (citations omitted). Likewise, the court stressed that claims must be read in light of the specification. *Id.* at 1315 ("claims must be read in view of the specification, of which they are a part.") (internal quotations omitted)). Importantly, the court held that claim terms should be given "*their broadest reasonable construction* 'in light of the specification as it would be interpreted by one of ordinary skill in the art.'" *Id.* at 1316 (citing *In re Am. Acad. of Sci. Tech. Ctr.*, 367 F.3d 1359, 1364 (Fed. Cir. 2004) (emphasis added).

The *Phillips* court repeated the venerable warning that one must "avoid the danger of reading limitations from the specification into the claim." 415 F.3d at 1323. With that warning in mind, the court described the two primary instances in which the specification can limit the meaning of claim terms. *First*, the patentee can choose to recite an explicit definition for a claim term in the specification. *Id.* at 1316. In that case it is said that the patentee has acted as his own lexicographer and the patentee's definition "governs." *Id. Second*, the specification may limit the plain meaning of a claim term when the patentee disclaims or disavows certain interpretations of the term. *Id.* In other words, the specification can limit the plain meaning of claim terms when the patentee has clearly set forth a limiting interpretation.

The prosecution history is also important to consider when construing claim terms. The *Phillips* court explained:

> [W]e have held that a court "should also consider the patent's prosecution history, if it is in evidence." . . . The prosecution history, which we have designated as part of the "intrinsic evidence," consists of the complete record of the proceedings before the PTO and includes the prior art cited during the examination of the patent. . . . Like the specification, the prosecution history provides evidence of how the PTO and the inventor understood the patent. . . . Furthermore, like the specification, the prosecution history was created by the patentee in attempting to explain and obtain the patent.

415 F.3d at 1317 (citations omitted).

The *Phillips* court also noted that expert testimony (on which Xoft almost exclusively relies in this case) should play a lesser role in claim construction. 415 F.3d at 1317 ("[W]hile extrinsic evidence 'can shed useful light on the relevant art,' we have explained that it is 'less significant than

the intrinsic record in determining the legally operative meaning of claim language.'") (internal quotations omitted). The court added that:

> extrinsic evidence in the form of expert testimony can be useful to a court for a variety of purposes, such as to provide background on the technology at issue, to explain how an invention works, to ensure that the court's understanding of the technical aspects of the patent is consistent with that of a person of skill in the art, or to establish that a particular term in the patent or the prior art has a particular meaning in the pertinent field. . . . However, conclusory, unsupported assertions by experts as to the definition of a claim term are not useful to a court. Similarly, *a court should discount any expert testimony "that is clearly at odds with the claim construction mandated by the claims themselves, the written description, and the prosecution history, in other words, with the written record of the patent."*

Id. at 1318 (emphasis added; citations omitted).

One claim limitation from the '813 patent uses the term "means," which creates a presumption that the limitation is drafted in "means plus function" format pursuant to 35 U.S.C. § 112, ¶ 6. *Greenberg v. Ethicon Endo-Surgery, Inc.*, 91 F.3d 1580, 1584 (Fed. Cir. 1996). "Construction of a means plus function limitation requires identification of the function recited in the claim and a determination of what structures have been disclosed in the specification that correspond to the means for performing that function." *Epcon Gas Sys., Inc. v. Bauer Compressors, Inc.*, 279 F.3d 1022, 1032 (Fed. Cir. 2002). Structure described in the specification constitutes "corresponding structure" if the specification "clearly links or associates that structure to the function recited in the claim." *Kahn v. General Motors Corp.*, 135 F.3d 1472, 1476 (Fed. Cir. 1998).

The Federal Circuit has held that a claim must be "definite" enough to be understood by one skilled in the art:

> We have stated the standard for assessing whether a patent claim is sufficiently definite to satisfy the statutory requirement as follows: If one skilled in the art would understand the bounds of the claim when read in light of the specification, then the claim satisfies section 112 paragraph 2.

Exxon Research & Eng'g Co. v. United States, 265 F.3d 1371, 1375 (Fed. Cir. 2001) (citing *Miles Labs., Inc. v. Shandon, Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993)). "If the meaning of the claim is discernible, even though the task may be formidable and the conclusion may be one over which reasonable persons will disagree, we have held the claim sufficiently clear to avoid invalidity on indefiniteness grounds." *Id. See also Fresenius Med. Care Holdings, Inc. v. Baxter Int'l, Inc.*, No. C

03-1431 SBA, 2006 U.S. Dist. LEXIS 36788, at *51 (N.D. Cal. May 24, 2006). As the party asserting invalidity, Xoft bears the burden of proving indefiniteness. Moreover, because patents enjoy a statutory presumption of validity, Xoft's burden is heightened – it must prove its case with clear and convincing evidence. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1375 (Fed. Cir. 1986). A claim is not indefinite merely because it poses a difficult issue of claim construction (which is not even the case here, where construction is straightforward); if the claim can be construed at all, then it is not invalid for indefiniteness. *See, e.g., Bancorp Servs., LLC v. Hartford Life Ins. Co.*, 359 F.3d 1367, 1371 (Fed. Cir. 2004). Thus, the biased, conclusory statements of Xoft's expert alone cannot establish indefiniteness by clear and convincing evidence. *See Intel Corp. v. VIA Techs.*, 319 F.3d 1357, 1367 (Fed. Cir. 2003) (expert's conclusory statements are insufficient to provide clear and convincing evidence of indefiniteness).

CONSTRUCTION OF CLAIM TERMS[2]

I. TERMS IN THE '813 PATENT

The claims of the '813 patent relate to an instrument comprising a concentric arrangement of an inner spatial volume and an outer spatial volume defined by an inflatable chamber, disposed near the distal end of a catheter body. One of the volumes contains a source of radiation, while the other volume may contain a radiation absorptive material. In one preferred embodiment, shown in Figure 1 of the patent, the inner volume is defined by an enclosed chamber surrounding the catheter body and containing a radioactive source. The outer chamber, concentric with the inner volume, is then inflated with air or other radiation absorbing material so that its wall contacts the wall of the surgical cavity substantially at all points. The distance between the radiation source and the wall of the outer chamber can be made constant. This embodiment permits the controlled delivery of radiation to a layer of tissue surrounding the surgical cavity.[3] By manipulating the volume and type of material in the outer

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[2] Cytyc addresses herein only those terms about which the parties disagree and which Cytyc believes to be material to resolution of this suit. As to terms not addressed, Cytyc's position is as set forth in the parties' Joint Claim Construction Statement, which Cytyc incorporates by reference herein.

[3] The tissue to be treated and the resected cavity can be thought of as an orange peel with the fruit (*i.e.*, the tumor) removed. A radiation source is placed within the space previously occupied by the fruit. The thickness of the "orange

(Continued...)

chamber, the ratio of the absorbed dose at the surface of the wall of tissue to the dose at the tissue depth where the minimum dose is prescribed to be received can be controlled so as to maximize the effectiveness of the treatment and minimize adverse side effects, namely, unwanted necrosis of healthy tissue.

The '813 patent teaches that other embodiments can be used to deliver therapeutic radiation to the layer of tissue surrounding the surgical cavity. (Col 2:64 – 4:20; FIGS. 3-5.) These other embodiments include the use of a radioactive liquid within an inner inflatable chamber, a plurality of radioactive solid particles, a slurry of a fluid containing particles of a radioactive isotope or a solid radioactive source. Alternatively, these same radiation sources can be placed in the volume of space between the inner chamber and the outer inflatable chamber. Any of these embodiments might be used as a means of delivering radiation to tissue within the wall of a surgical cavity.

A. "Inner Spatial Volume" (All Asserted Claims)

Cytyc's Proposed Construction	Xoft's Proposed Construction
A region of space surrounded by an outer spatial volume that is defined by a closed inflatable chamber.	Inner balloon in two-balloon device or spherical solid radionuclide in one-balloon device.

Xoft's attempt to limit the "inner spatial volume" to a "balloon" or a "spherical solid radionuclide" should be rejected. As an initial matter, a "balloon" is not even one of the embodiments of the "inner spatial volume" described in the specification. Rather, the specification describes, as an exemplary embodiment, that "the inner spatial volume 30 . . . *may* be defined by a generally spherical polymeric film wall 32." (Col. 2:35-36 (emphasis added).) In any event, it is improper to limit the claim language to the embodiments in the specification, as Xoft proposes. *Phillips*, 415 F.3d at 1323 ("For instance, although the specification often describes very specific embodiments of the invention, we have repeatedly warned against confining the claims to those embodiments.").

(...Continued)

peel" corresponds to the thickness of the tissue to be treated – in most procedures the "orange peel" of tissue to be treated is about 2 centimeters thick. (*See, e.g.*, '813 patent at FIG. 4.)

More fundamentally, Xoft confuses the tangible structure that defines the inner spatial volume with the volume itself. The specification provides that the inner spatial volume 30 "may be *defined by* a generally spherical polymeric film." The film defines the boundary of the volume but the volume is the region of space within that boundary. (Exhibit C to the Declaration of Henry C. Su (American Heritage College Dictionary ("AHC")) at 1513.) Thus, according to the specification, the inner spatial volume is simply a region of space surrounded by an outer spatial volume. (*See* col. 1:52-55 ("a first spatial volume at the distal end of a catheter and a second spatial volume defined by a surrounding of the first spatial volume by a polymeric film wall . . . .").)

Cytyc's proposed construction fully captures the plain meaning of "inner spatial volume," which the Federal Circuit notes is of "primary importance" in claim construction. *Phillips*, 415 F.3d at 1312. A "spatial volume" is a commonly understood English term, meaning simply "a region of space." (AHC at 1513.) The word "inner" means that that region of space is located within something else, and the specification provides that that "something else" is another (outer) "spatial volume." (Col. 1:52-55.) "Inner spatial volume" should therefore be construed to mean "a region of space surrounded by an outer spatial volume that is defined by a closed inflatable chamber."

B. "Outer, Closed, Inflatable Chamber" (All Asserted Claims)

Cytyc's Proposed Construction	Xoft's Proposed Construction
No construction required or appropriate.	Inflatable balloon, i.e., deflated balloon.

Cytyc believes that no construction of this term is required or appropriate. The term has its ordinary and customary meaning to one skilled in the art without reference to intrinsic or extrinsic evidence. There is no evidence of any intent by the inventors to impart a novel or special meaning to the term and Xoft has pointed to none. As discussed above with respect to an "inner spatial volume," Xoft's construction improperly attempts to limit the claim term to just a balloon. But nothing in the specification limits the outer, closed inflatable chamber to a "balloon." Xoft's proposed construction is not supported by the specification and is contrary to law. Cytyc proposes the term be given its plain meaning: an "outer, closed, inflatable chamber." Examples of such a chamber include an inflatable balloon or an expandable cage, and as Dr. Verhey points out, an "inflatable chamber of any type"

could satisfy this limitation. This, Xoft's proposed construction should be rejected and the plain meaning of the term adopted.

C. "Predetermined Constant Spacing" (All Asserted Claims)

Cytyc's Proposed Construction	Xoft's Proposed Construction
No construction required or appropriate.	Indefinite. "Predetermined" spacing is some undefined constant spacing predetermined in some undefined manner with regard to deflated outer chamber.

Cytyc addresses the construction of this term in connection with its construction of the term "a predetermined constant spacing between said inner spatial volume and the radiation transparent wall" below. Cytyc believes that a separate construction of this term divorced from the context of the surrounding claim language is neither required nor appropriate. *See Phillips*, 415 F.2d at 1314 ("Quite apart from the written description and the prosecution history, the claims themselves provide substantial guidance as to the meaning of particular claim terms. . . . To begin with, the context in which a term is used in the asserted claim can be highly instructive.") (citing *ACTV, Inc. v. Walt Disney Co.*, 346 F.3d 1082, 1088 (Fed. Cir. 2003) ("the context of the surrounding words of the claim also must be considered in determining the ordinary and customary meaning of those terms")).

Xoft proposes no construction of this term, arguing that it is indefinite. Contrary to Xoft's assertion, the term "predetermined constant spacing" is not indefinite and has an ordinary and customary meaning to one skilled in the art. Dr. Verhey easily understood the phrase "predetermined constant spacing" – indeed, any speaker of English can understand it – to mean that the spacing between the inner spatial volume and the wall of the outer inflatable chamber is made to be substantially constant. This spacing is "predetermined" in the sense that it is chosen in advance by one skilled in the art. (Exhibit C at 1077.) Although Xoft incorrectly suggests that the patent must describe that amount of spacing, a patent does not need to describe what one skilled in the art already knows. *See S3 Inc. v. nVidia Corp.*, 259 F.3d 1364, 1371 (Fed. Cir. 2001) ("The law is clear that patent documents need not include subject matter that is known in the field of the invention and is in the prior art, for patents are written for persons experienced in the field of the invention. . . . To hold

otherwise would require every patent document to include a technical treatise for the unskilled reader.") (citation omitted). One skilled in the art knows how to determine an appropriate "predetermined constant spacing." Xoft cannot possibly show that the term is indefinite by clear and convincing evidence.

D. "Predetermined Constant Spacing Between Said Inner Spatial Volume And The Radiation Transparent Wall" (All Asserted Claims)

Cytyc's Proposed Construction	Xoft's Proposed Construction
The spacing between the inner spatial volume and the radiation transparent wall of the outer, closed, inflatable chamber, when inflated, can be made constant in all directions if the outer chamber is spherical, or constant along a radial plane if the outer chamber is not spherical.	Indefinite. *See* "predetermined constant spacing," *supra*, § I.C.

Xoft proposes no construction of this term, arguing only that it is indefinite. The conclusory statement of Dr. Lovoi, who works for Xoft and thus cannot provide a neutral opinion, does not come close to providing the clear and convincing evidence needed for Xoft to show indefiniteness. To the contrary, the term is readily understood by those skilled in the art. As Dr. Verhey explains, the term means that the spacing between the inner spatial volume and the radiation transparent wall of the outer, closed inflatable chamber, when inflated, can be made constant. If the outer chamber is spherical, then the distance is constant in all directions. If the outer chamber is cylindrical, then the distance is constant around a radial plane that is perpendicular to the axis of the catheter. (Verhey Rep. at 7:2-5.) This plain meaning construction should be adopted. *Phillips*, 415 F.3d at 1312 (plain meaning is of "primary importance").

E. "Rendering Uniform" (All Asserted Claims)

Cytyc's Proposed Construction	Xoft's Proposed Construction
No construction required or appropriate.	Making the same, i.e., causing to have the same value or characteristic at all points.

Cytyc addresses the construction of this term in connection with its construction of the term "means . . . for rendering uniform the radial absorbed dose profile of the emissions" below. Cytyc

believes that a separate construction of this term divorced from the context of the surrounding claim language is neither required nor appropriate. *See Phillips*, 415 F.3d at 1314.

F. "Means . . . For Rendering Uniform The Radial Absorbed Dose Profile Of The Emissions " (All Asserted Claims)

Cytyc's Proposed Construction	Xoft's Proposed Construction
Disputed Function: Modifying the ratio of the absorbed dose at a depth of interest in the target tissue to the absorbed dose at the surface of the tissue.	*Disputed Function*: Making the dose along a radius extending from the radionuclide outwardly from the outer chamber wall the same at every point on the radius.
Disputed Structure: A radiation absorbing or attenuating material, *e.g.*, air, x-ray contrast fluid, contrast media used in angiography, water, a gas, or barium sulfite.	*Disputed Structure*: No such means disclosed in the '813 patent, means for making more uniform disclosed as substance within outer chamber.

Because this is a "means-plus-function" limitation subject to 35 U.S.C. § 112, ¶ 6, the Court must construe the limitation's function as well as the structure disclosed in the specification that corresponds to that function. *BBA Nonwovens Simpsonville, Inc. v. Superior Nonwovens, L.L.C.*, 303 F.3d 1332, 1343 (Fed. Cir. 2002) (Construction of a means-plus-function limitation "requires the court to first identify the function of the means-plus-function limitation and next identify the corresponding structure in the written description necessary to perform that function."). The function required by this limitation is "rendering uniform the radial absorbed dose profile of the emissions." As Dr. Verhey explains, the radial absorbed dose profile is defined as the absorbed dose in tissue, varying as a function of distance from the center of the cavity along a particular direction of interest. (Verhey Rep. at 6:21-23.) In the '813 patent, the direction of interest would be from the wall of the surgical cavity to a depth in the target tissue at which a prescribed therapeutic dose is defined. (*Id.*) These profiles are shown as lines 40 and 42 in the '813 patent at Figure 4, reproduced on the next page and annotated for discussion purposes:

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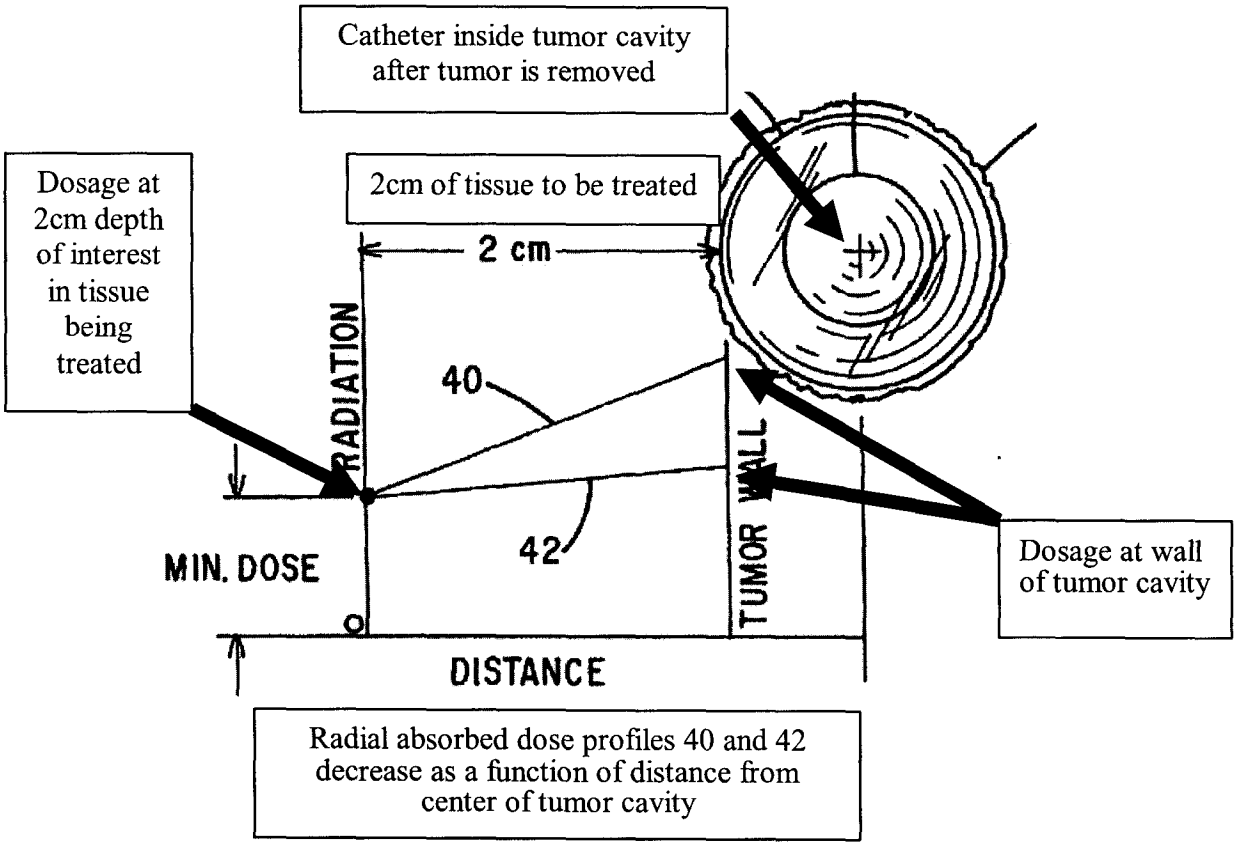

The patentees have defined in the specification what they mean by "rendering uniform the radial absorbed dose profile of the emissions." *Phillips*, 415 F.3d at 1316 (claims must be read in light of the specification). In Figure 4, line 40 is a plot of the absorbed dose as a function of radial distance that would be obtained if there were no structure defining an inner volume, *i.e.*, if the entire spherical volume of the tumor were completely filled with radioactive fluid. (Col. 3:20-24.) Plot 42, by contrast, shows the absorbed dose as a function of radial distance when the radioactive fluid is contained within an inner volume (defined by a polymeric film wall) and is surrounded by a radiation absorbing material contained in the outer volume. (Col. 3:24-28.) According to the specification, "[c]omparing plots 40 and 42, by providing the concentric arrangement depicted, the absorbed dose profile in the space between the 2cm site and the wall of the outer balloon is maintained *much more uniform*, thus preventing over-treatment of body tissue at or close to the outer wall 36 of the instrument." (Col. 3:28-33 (emphasis added).) As Dr. Verhey explains, plot 42 in Figure 4 shows a smaller ratio of the absorbed dose at the wall of the tumor cavity to the dose at the 2cm depth of interest than plot 40. Thus, as the specification defines the term, "rendering uniform the radial

absorbed dose profile of the emissions" means modifying the ratio of the absorbed dose at a depth of interest in the target tissue to the dose at the surface of the tissue, as exemplified by the difference between the slopes of plots 40 and 42.

Xoft's construction of this function is unreasonable because it excludes the preferred embodiments shown in the specification. "A claim construction that excludes a preferred embodiment . . . is 'rarely, if ever, correct.'" *Pfizer, Inc. v. Teva Pharms.USA, Inc.*, 429 F.3d 1364, 1374 (Fed. Cir. 2005) (quoting *SanDisk Corp. v. Memorex Prods., Inc.*, 415 F.3d 1278, 1285 (Fed. Cir. 2005)); *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1583 (Fed. Cir. 1996) (same). In the diagram in Figure 4, the radial absorbed dose profile plot 42 does not show the same dose at every point along the radius, as Xoft would require. Rather, the ratio of the dose at the cavity wall to the dose at the depth of interest is less than that for the configuration in plot 40, consistent with Cytyc's construction.

The corresponding structure disclosed in the specification for performing this function is a radiation absorbing or attenuating material, *e.g.*, air, x-ray contrast fluid, contrast media used in angiography, water, a gas, or barium sulfite. *Kahn*, 135 F.3d at 1476 (holding that structure described in the specification is corresponding structure if the specification "clearly links or associates that structure to the function recited in the claim."). Xoft appears to agree, suggesting that the "substance within the outer chamber" corresponds to the function for making the radial absorbed dose profile more uniform.

G. "The Radioactive Material" (Claim 8)

Cytyc's Proposed Construction	Xoft's Proposed Construction
The material of claim 1 containing a radionuclide.	Indefinite because no antecedent.

Again, Xoft offers no construction of this term, arguing only that it is indefinite. Xoft's argument fails. Claim 8 depends from claim 1, and it is obvious that the "the radioactive material" in claim 8 clearly refers back to "a material containing a radionuclide" described in claim 1, given that the "radionuclide" is the only radioactive material mentioned in claim 1. Anyone skilled in the art

would know that the "radioactive material" in claim 8 refers to the "material containing a radionuclide" in claim 1. Claim 8 is therefore not indefinite.

H. "A Plurality Of Radioactive Solid Particles Placed At Pre-determined Locations Within The Inner Spatial Volume To Provide A Desired Composite Radiation Profile" (Claim 12)

Cytyc's Proposed Construction	Xoft's Proposed Construction
A plurality of radioactive solid particles placed at pre-determined locations within the inner spatial volume to provide a desired dose profile that is the sum of the radiation profiles of the plurality of particles.	Static array of solid radioactive particles each placed in a single location and mounted on distal ends of separate wires. "Desired composite radiation profile" is indefinite.

Xoft's proposed construction of this term improperly imports limitations from the specification that are merely examples of the preferred embodiment. The ordinary meaning of this claim term, which Cytyc proposes as the proper construction here, follows the language of the claim: "A plurality of radioactive solid particles placed at pre-determined locations within the inner spatial volume to provide a desired dose profile that is the sum of the radiation profiles of the plurality of particles." (*See* AHC at 286 (defining composite as "made up of distinct components; compound").)

II. TERMS IN THE '204 PATENT

The '204 patent, which is a continuation-in-part of the '813 patent, describes an apparatus for brachytherapy and a method of using it for interstitial delivery of radiation to diseased cells within the interstices of the tissue surrounding the cavity created by the surgical removal of proliferative tissue. The apparatus includes a catheter body member having a proximal end and a distal end, an inner spatial volume proximate to the distal end of the catheter body member, an outer spatial volume defined by an expandable surface element proximate to the distal end of the body member, and surrounding and concentric with the inner spatial volume. In a preferred embodiment, a radiation source is disposed within the inner spatial volume.

The '204 patent describes a number of embodiments that can be used in the apparatus for delivering a therapeutic dose of radiation, including, without limitation, radioactive microspheres (FIG. 4), concentric non-spherical chambers (FIG. 5), a single solid radiation emitting material surrounded by an expandable cage defining the shape of the tumor cavity (FIG. 6), a radioactive fluid filling the

outer chamber (FIG. 7a), a radioactive fluid filling the inner chamber and the outer chamber filled with air or other radiation absorbing substance (FIG. 7b), and a single solid source surrounded by an outer chamber filled with a radiation absorbing substance (FIG. 7c). Figure 7d shows examples of radiation profiles which might be obtained by the embodiments shown in Fig. 7a-7c where the depth of interest is shown as 2cm from the surface of the outer volume. As can be seen, different embodiments can be used to vary the ratio of the dose at the prescribed depth to the dose at the wall of the cavity.

A. "Interstitial" (All Asserted Claims)

Cytyc's Proposed Construction	Xoft's Proposed Construction
No construction required or appropriate.	Site in natural or surgically created cavity in body.

Cytyc addresses the construction of this term in connection with its construction of the term "interstitial brachytherapy" below. Cytyc believes that a separate construction of this term divorced from the context of the surrounding claim language is neither required nor appropriate. *See Phillips*, 415 F.3d at 1314.

B. "Brachytherapy" (All Asserted Claims)

Cytyc's Proposed Construction	Xoft's Proposed Construction
Radiation therapy delivered by a spatially confined radiation source at or near the site of the diseased tissue.	Radiation therapy delivered by a spatially confined radionuclide at or near a tumor or other proliferative tissue disease site.

The parties mostly agree on the definition of "brachytherapy" with two exceptions. *First*, Xoft attempts to limit brachytherapy to the use of a "radionuclide" for irradiating tissue. But radiation can be provided from sources that are not radionuclides (but that can be equivalent to radionuclides), *e.g.* an X-ray tube. (*See* Exhibit F to the Declaration of Henry C. Su (The Physics of Radiation Therapy) at 418 ("Brachytherapy is a method of treatment in which sealed radioactive sources are used to deliver radiation at a short distance by interstitial, intracavitary, or surface application.").) There is no reason to limit brachytherapy to use of a radionuclide and Xoft's construction should be rejected. *Second*, Xoft improperly attempts to limit brachytherapy to treatment of tumors or other proliferative tissue

diseases. But there is no basis for such a limitation, as radiation can be applied to any diseased tissue as a doctor believes appropriate.

C. "Interstitial Brachytherapy" (All Asserted Claims)

Cytyc's Proposed Construction	Xoft's Proposed Construction
Brachytherapy applied directly to the interspaces of a body tissue, where the interspaces are not naturally occurring.	Radiation therapy delivered by a spatially confined radionuclide at or near a tumor site in a natural or surgically resected cavity in a body.

Xoft has, for almost all the other disputed terms in the '204 patent, improperly added limitations that are not supported by the terms' plain meaning or the patent specification or prosecution history. With respect to "interstitial brachytherapy," which the inventors specifically defined in the prosecution history as excluding certain types of therapies, Xoft now improperly redefines the term in a manner inconsistent with the inventors' clear statements. Xoft may not blithely ignore the intrinsic evidence.

Specifically, Xoft's attempt to include "natural" body cavities in its definition of "interstitial brachytherapy" is directly contrary to the patent's prosecution history. During prosecution of the '204 patent, in traversing a rejection from the examiner, the inventors distinguished between brachytherapy applied to a natural body cavity and interstitial brachytherapy:

> Turning to the cited prior art, the Ishiwara device comprises a thermotherapeutic apparatus having a catheter body member, an inner lumen surrounded by an outer lumen, and a radiation source contained within the inner lumen. As disclosed in col. 4, lines 19-23, Ishiwara's apparatus is inserted into a body cavity. . . . Hence the apparatus does not provide *interstitial* radiation treatment, as Applicant's invention requires, but rather intercavital radiation treatment.

(Exhibit E to the Declaration of Henry C. Su (12/20/00 Amendment and Response ("Amendment")) at 11 (emphasis in original; internal citations omitted).)

Similarly, with respect to another reference, the inventors distinguished intraluminal therapy from interstitial therapy:

> Weinberger discloses in Figure 17 an intercavital radiotherapy device for insertion within a patient's lumen. . . . Like Ishiwara, Weinberger's apparatus does not provide *interstitial* radiation treatment, as Applicant's invention requires, but instead *intraluminal* radiation treatment. Whereas Applicant's device treats disease that is

> embedded in tissue (e.g., breast cancer), Ishiwara and Weinberger treat disease in a luminal cavity. For this reason, in Ishiwara and Weinberger, the catheters and expandable balloons are very different than those of Applicant's invention.

(Amendment at 12 (emphasis in original; internal citations omitted).) In light of these clear statements, Cytyc is surprised that Xoft would even attempt to propose a construction of "interstitial brachytherapy" that included natural body cavities or lumens.

In summary, the inventors have specifically excluded "intercavital" or "intraluminal" radiation therapy – *i.e.,* insertion of a brachytherapy apparatus within a natural body cavity or lumen – from the definition of "interstitial brachytherapy." Cytyc's proposed construction comports with the plain meaning of the claim term, based on the inventors' disclaimer in the prosecution history.

D. "Inner Spatial Volume" (All Asserted Claims)

Cytyc's Proposed Construction	Xoft's Proposed Construction
.A region of space surrounded by an outer spatial volume that is defined by an expandable surface element.	Inner balloon in two-balloon device or spherical solid radionuclide in one-balloon device.

Xoft's attempt to limit the "inner spatial volume" to a "balloon" or a "spherical solid radionuclide" should be rejected. A "balloon" is not even one of the embodiments of the "inner spatial volume" described in the specification. Rather, as in the '813 patent, the specification of the '204 patent describes, as an exemplary embodiment, that "the inner spatial volume 30 . . . ***may*** be defined by a generally spherical polymeric film wall 32." (Col. 3:58-59.) In any event, it is improper to limit the claim language to the embodiments in the specification, as Xoft proposes. *Phillips*, 415 F.3d at 1323 (one must "avoid the danger of reading limitations from the specification into the claim.").

More fundamentally, Xoft continues to confuse the structure that defines an inner spatial volume with the volume itself. The specification provides that the inner spatial volume 30 "may be *defined by* a generally spherical polymeric film." The film defines the boundary of the volume but the volume is the region of space within that boundary. Thus, according to the specification, the inner spatial volume is simply a region of space surrounded by an outer spatial volume. (*See* col. 2:39-45 ("The apparatus includes . . . an inner spatial volume disposed proximate to the distal end of the catheter body member, [and] an outer spatial volume defined by an expandable surface element

disposed proximate to the distal end of the body member in a surrounding relation to the inner spatial volume . . . .").)

Cytyc's proposed construction fully captures the plain meaning of "inner spatial volume," which the Federal Circuit notes is of "primary importance" in claim construction. *Phillips,* 415 F.3d 1312. A "spatial volume" is a commonly understood English term, meaning "a region of space." (AHC at 1513 (defining "volume" as "the amount of space occupied by a three-dimensional object or region of space, expressed in cubic units").) The word "inner" means that that region of space is located within something else, and the specification provides that that "something else" is another (outer) "spatial volume." (Col. 1:52-55.) Thus, "inner spatial volume" should be construed to mean "a region of space surrounded by an outer spatial volume that is defined by a closed inflatable chamber."

E. "Outer Spatial Volume" (All Asserted Claims)

Cytyc's Proposed Construction	Xoft's Proposed Construction
No construction required or appropriate. Alternatively: a region of space defined by an expandable surface element and surrounding an inner spatial volume.	Balloon or cage.

Cytyc believes that no construction of this term is required or appropriate. The term has its ordinary and customary meaning to one skilled in the art without reference to intrinsic or extrinsic evidence, and there is no evidence of any intent by the inventors to impart a novel or special meaning to the term. Thus, "outer spatial volume" should be construed to mean "outer spatial volume."

Xoft's proposed construction of the term, like its proposed construction of "inner spatial volume," confuses the outer spatial volume with the "expandable surface element" that defines its boundary. The "outer spatial volume" is a region of space that is *defined* by an "expandable surface element" but it is not the "expandable surface element" itself. (*See* col. 3:61-65.) If the Court is inclined to construe "outer spatial volume," then the term should be construed as "a region of space defined by an expandable surface element and surrounding an inner spatial volume." This is consistent with the ordinary meaning of the claim term in view of the specification.

F. "Expandable Surface Element" (All Asserted Claims)

Cytyc's Proposed Construction	Xoft's Proposed Construction
No construction required or appropriate. Alternatively: a device that can be expanded or inflated, such as an expandable cage or an inflatable balloon.	Deflated balloon or collapsed cage.

Cytyc believes that no construction of this term is required or appropriate. The term has its ordinary and customary meaning to one skilled in the art without reference to intrinsic or extrinsic evidence, and there is no evidence of any intent by the inventors to impart a novel or special meaning to the term. "Expandable surface element" should be construed to mean "expandable surface element."

Xoft's attempt to limit the term to a "deflated balloon or a collapsed cage" is improper, and there is no support for doing so in any of the intrinsic evidence. Something that is "expandable" is capable of expansion (or inflation) and can be in any state of expansion (or inflation) from no expansion to full expansion. Indeed, as Dr. Verhey explains, a person having ordinary skill in the art would expect to have to expand the expandable surface element in order to practice the invention of the '204 patent. (Verhey Rep. at 9:17-20, 10:16-18.) A construction that limits this element to a "deflated" or "collapsed" state is unreasonable and erroneous.

G. "Radiation Source" (All Asserted Claims)

Cytyc's Proposed Construction	Xoft's Proposed Construction
No construction required or appropriate.	Radionuclide

Cytyc believes that no construction of this term is required or appropriate. The term has its ordinary and customary meaning to one skilled in the art without reference to intrinsic or extrinsic evidence, and there is no evidence of any intent by the inventors to impart a novel or special meaning to the term. A "radiation source" is simply that—a radiation source. Xoft's attempt to limit a "radiation source" to just radionuclides, a specific kind of source, is unsupportable.

H. "Minimum Prescribed Dose" (Claims 2, 18, 24, 32, & 36)

Cytyc's Proposed Construction	Xoft's Proposed Construction
Minimum prescribed dose received within a target tissue for delivering therapeutic effects.	Minimum dose needed to treat cancer cells.

Xoft's attempt to limit this term to the provision of a dose to treat cancer cells is improper and unsupported. The term has its ordinary and customary meaning to one skilled in the art without reference to intrinsic or extrinsic evidence, and there is no evidence of any intent by the inventors to impart a novel or special meaning to the term. The meaning can be readily discerned from the context of the surrounding claim language – "a minimum prescribed absorbed dose for delivering therapeutic effects to a target tissue." (*See, e.g.*, col. 8:31-33.) *See also Phillips,* 415 F.3d at 1314 ("Quite apart from the written description and the prosecution history, the claims themselves provide substantial guidance as to the meaning of particular claim terms. . . . To begin with, the context in which a term is used in the asserted claim can be highly instructive.")

I. "Delivering A Prescribed Absorbed Dose" (Claim 34)

Cytyc's Proposed Construction	Xoft's Proposed Construction
No construction required or appropriate.	Indefinite – the patent contains no information on how to obtain a prescribed dose, much less a prescribed dose using an expandable surface element.

Cytyc believes that no construction of this term is required or appropriate. The term has its ordinary and customary meaning to one skilled in the art without reference to intrinsic or extrinsic evidence, and there is no evidence of any intent by the inventors to impart a novel or special meaning to the term. Contrary to Xoft's assertion, the phrase is not indefinite because a "prescribed absorbed dose" refers to the fact that the amount of the dose to be delivered to a target tissue is within the discretion (i.e., prescription) of a person with ordinary skill in the art to determine. For example, a radiation oncologist determines, using treatment planning software or some other reference or tool, the proper dosage for each patient, depending on a number of physiological factors. The patient-specific

amount of radiation is a "prescribed dose." As to how the dose is delivered, Dr. Verhey explains that "once the inflatable expandable surface element is in contact with the surface of the surgical cavity, the dose at the prescription depth can be delivered once the radiation source is introduced into the catheter." (Verhey Rep. at 9:26-28 (citing col. 5:66 – 6:28).) Delivering a prescribed absorbed dose is not indefinite and the term means exactly what it says—delivering a prescribed absorbed dose.

J. "The Inner And Outer Spatial Volumes Are Configured To Provide A Minimum Prescribed Absorbed Dose" (Claim 2 & 36) And "Configuring The Inner And Outer Spatial Volumes To Provide A Minimum Prescribed Absorbed Dose" (Claims 24 & 32)

Cytyc's Proposed Construction	Xoft's Proposed Construction
The inner and outer spatial volumes are configured to provide a minimum prescribed absorbed dose for delivering therapeutic effects to a target tissue; and Configuring the inner and outer spatial volumes to provide a minimum prescribed absorbed dose for delivering therapeutic effects to a target tissue.	Indefinite – configured volumes are expanded volumes, but no cause and effect relationship between configuring of inner and outer volumes and providing dose of any prescribed amount.

Contrary to Xoft's contention, this term is not indefinite. The '204 patent discloses in detail the various ways in which a person of ordinary skill in the art can achieve a configuration of the inner and outer spatial volumes that will deliver a minimum prescribed dose to a target tissue of interest. (*See, e.g.,* col. 5:22-41; col. 6:16 – col. 7:28.) As Dr. Verhey explains:

> [W]here the radioactive material is disposed in the inner spatial volume, the rate at which the dose falls off between the surface of the surgical cavity and the depth at which the minimum dose is to be prescribed, can be controlled by modifying the quantity and type of radiation absorbing material contained within the outer spatial volume. The safe delivery of the minimum prescribed dose at the depth of interest requires that the tissue intervening between the surface of the cavity and the depth of interest receive a dose which is equal to or grater than the prescribed dose but less than that which would necrose (i.e., lethally damage) healthy tissue."

(Verhey Rep. at 8:25 – 9:3.) Because one skilled in the art knows how to configure the spatial volumes to provide the minimum prescribed absorbed dose, the term is not indefinite.

K. "A Minimum Distance Outward From The Outer Spatial Volume Expandable Surface" (Claims 2, 24, 32, & 36)

Cytyc's Proposed Construction	Xoft's Proposed Construction
No construction required or appropriate.	Indefinite because it is some unknown distance from deflated balloon or collapsed cage. Patent contains no information regarding determination of minimum distance.

Cytyc believes that no construction of this term is required or appropriate and that the term is definite. The term has its ordinary and customary meaning and is understood by one of ordinary skill in the art without reference to intrinsic or extrinsic evidence, and there is no evidence of any intent by the inventors to impart a novel or special meaning to the term.

The meaning of "a minimum distance outward from the outer spatial volume expandable surface" is not indefinite and can be readily discerned from the context of the surrounding claim language – "the target tissue being defined between the outer spatial volume expandable surface and a minimum distance outward from the outer spatial volume expandable surface." The disputed phrase refers to the minimum distance outward from the expandable surface element that defines the outer spatial volume. This minimum distance defines the thickness of a layer of target tissue which, in the determination of a person of ordinary skill in the art, includes the region in which diseased cells might reside. (Verhey Rep. at 9:6-9.)

L. "Controlled Dose" (Claim 2, 24, 32, & 36)

Cytyc's Proposed Construction	Xoft's Proposed Construction
No construction required or appropriate.	Indefinite because configuration, i.e., expansion, of inner and outer volumes does not control dose.

Cytyc addresses the construction of this term in connection with its construction of the phrase "providing a controlled dose at the outer spatial volume expandable surface to reduce or prevent necrosis in healthy tissue proximate to the expandable surface" below. Cytyc believes that a separate

construction of this term divorced from the context of the surrounding claim language is neither required nor appropriate.

M. "To Reduce Or Prevent Necrosis In Healthy Tissue Proximate To The Expandable Surface" (Claims 2, 24, 32, & 36)

Cytyc's Proposed Construction	Xoft's Proposed Construction
No construction required or appropriate.	Indefinite – patent does not describe providing a dose through expandable surface – improper functional limitation in apparatus claim.

Cytyc addresses the construction of this term in connection with its construction of the phrase "providing a controlled dose at the outer spatial volume expandable surface to reduce or prevent necrosis in healthy tissue proximate to the expandable surface" below. Cytyc believes that a separate construction of this term divorced from the context of the surrounding claim language is neither required nor appropriate.

N. "Providing A Controlled Dose At The Outer Spatial Volume Expandable Surface To Reduce Or Prevent Necrosis In Healthy Tissue" (Claims 2, 24, 32 & 36)

Cytyc's Proposed Construction	Xoft's Proposed Construction
Controlling the ratio of the dose at the expandable surface of the outer spatial volume to the prescribed dose at the depth of interest in the target issue so that the dose at the expandable surface is not so high that it lethally damages cells in healthy tissue in contact with the expandable surface	Indefinite because radiation dose is not provided when outer volume surface is "expandable", i.e., is a deflated balloon or a collapsed cage. Also indefinite because patent contains no information on how to provide dose that will reduce or prevent necrosis in healthy tissue. In context, the word "necrosis" and the term "necrosis in healthy tissue" are indefinite.

Xoft does not offer a construction of this disputed term; it only argues that the term is indefinite. But the term is well understood by those of skill in the art. Dr. Verhey explains that by adjusting the distance between the radiation source and the surface of the outer spatial volume, or by adjusting the type of radiation absorbing material in the outer spatial volume, the ratio of the dose at the surface of the outer spatial volume to the prescribed dose at the depth of prescription can be

controlled. (Verhey Rep. at 9:12-15.) The dose must not be so high that it causes necrosis to occur in healthy tissue that is in contact with the expandable surface; persons of skill in the art will know how high such a dose may be before a significant percentage of healthy cells necrose. (*Id.*)

O. "Adapting The Expandable Surface To Contact Tissue Surrounding The Resection Cavity To Conform The Tissue" (Claim 34)

Cytyc's Proposed Construction	Xoft's Proposed Construction
No construction required or appropriate.	Indefinite because expandable surface, i.e., deflated balloon or collapsed cage, neither contacts nor conforms the tissue surrounding the resection cavity. The patent contains no information on how this could be done.

Cytyc believes that no construction of this term is required or appropriate and that the term is definite. The term has its ordinary and customary meaning and is understood by one of ordinary skill in the art without reference to intrinsic or extrinsic evidence, and there is no evidence of any intent by the inventors to impart a novel or special meaning to the term. The term "adapting the expandable surface to contact tissue surrounding the resection cavity to conform the tissue to the desired shape of the expandable surface element" means adapting the expandable surface so that it comes into contact with the tissue forming the wall of the resection cavity and conforms that tissue to its shape. This comports with the ordinary meaning of the claim term.

Xoft's indefiniteness assertion is premised on its flawed construction of "expandable surface," which requires that the surface be in a deflated or collapsed state. The fact that claim 34, however, requires the expandable surface to contact the tissue surrounding the resection cavity establishes that Xoft's construction of "expandable surface" is erroneous. Under a proper construction, the expandable surface can be inflated or expanded to some degree so that it contacts the tissue and conforms the tissue to its shape. Dr. Verhey explains: "the volume of the expandable surface can be adjusted by inflation until the surface of the expandable volume is in contact with the surface of the resection cavity at all points. In this state, the shape of the resection cavity conforms to the shape of the expandable surface." (Verhey Rep. at 9:18-20 (citing col. 5:47-61).)

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P. "Desired Shape Of The Expandable Surface Element" (Claims 4, 26, & 34)

Cytyc's Proposed Construction	Xoft's Proposed Construction
The desired shape of the expandable surface element.	Indefinite. Patent contains no information regarding the desired shape of an expandable surface element, i.e., a deflated balloon or collapsed cage.

Cytyc believes that no construction of this term is required or appropriate and that the term is definite. The term has its ordinary and customary meaning and is understood by one of ordinary skill in the art without reference to intrinsic or extrinsic evidence, and there is no evidence of any intent by the inventors to impart a novel or special meaning to the term.

This term is not indefinite, as Xoft wrongly contends. The desired shape of the balloon is within the discretion of those skilled in the art. According to Dr. Verhey, "the desired shape of the expandable surface element is that shape which provides the predetermined constant spacing between the inner spatial volume and the conformed surface of the resection cavity." (Verhey Rep. at 9:22-24 (citing col. 5:47-61).) Examples of desired shapes described in the specification include a spherical balloon (FIG. 1) and a cylindrical balloon (FIG. 5), but the invention is not limited to any particular shape. (Col. 5:13-16.)

Q. "Predetermined Spacing" (Claims 3 & 25)

Cytyc's Proposed Construction	Xoft's Proposed Construction
No construction required or appropriate.	Indefinite because no information in patent re how to determine "predetermined spacing." Also indefinite because spacing is between inner spatial volume and expandable surface element, i.e., deflated balloon or collapsed cage.

Cytyc addresses the construction of this term in connection with its construction of the phrase "a predetermined spacing is provided between said inner spatial volume and the expandable surface element" below. Cytyc believes that a separate construction of this term divorced from the context of the surrounding claim language is neither required nor appropriate.

R. "A Predetermined Spacing Is Provided Between Said Inner Spatial Volume And The Expandable Surface Element"/ "A Predetermined Spacing Between Said Inner Spatial Volume And The Expandable Surface Element" (Claims 3 & 25)

Cytyc's Proposed Construction	Xoft's Proposed Construction
The distance between the inner spatial volume and the expandable surface element is determined in advance.	A predetermined spacing between inner spatial volume and deflated balloon or collapsed cage is indefinite.

Cytyc believes that no construction of this term is required or appropriate and that the term is definite. The term has its ordinary and customary meaning and is understood by one of ordinary skill in the art without reference to intrinsic or extrinsic evidence, and there is no evidence of any intent by the inventors to impart a novel or special meaning to the term.

Contrary to Xoft's assertion, the term is not indefinite and has an ordinary and customary meaning to one skilled in the art. Dr. Verhey readily understood the term to mean that the spacing between the inner and outer volumes can be set to a predetermined value by modifying the level of inflation or expansion of one or both volumes. Although Xoft incorrectly suggests that the patent must describe that amount of spacing, a patent does not need to describe what one skilled in the art already knows and can practice. *See S3 Inc. v. nVidia Corp.*, 259 F.3d 1364, 1371 (Fed. Cir. 2001). One skilled in the art knows how to determine an appropriate "predetermined spacing."

Moreover, to the extent Xoft contends that there can be no spacing between the inner volume and a deflated balloon or collapsed cage, that argument also fails. Such an argument is premised on the erroneous proposal that "expandable surface" be limited to a deflated or collapsed surface. Because that construction is inconsistent with the patent and must be rejected for the reasons set forth above (*see supra* at II.F), Xoft's indefiniteness argument must also fail.

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S. "Intraoperatively" (Claims 19 & 34)

Cytyc's Proposed Construction	Xoft's Proposed Construction
Intraoperatively Alternatively: during the surgical operation to remove proliferative tissue	After surgical removal of tumor but prior to closing the surgical site.

The parties appear to agree for the most part as to the meaning of "intraoperatively," and Cytyc could agree to Xoft's proposed construction if only the construction does not include "closing the surgical site," which is superfluous. "Intraoperatively" simply means during the surgical operation to remove the proliferative tissue. Whether the site is subsequently closed (*e.g.*, with sutures) is irrelevant.

T. "Solid Radiation Source" (Claim 16)

Cytyc's Proposed Construction	Xoft's Proposed Construction
A radiation source that has a fixed shape and volume, and is not deformable.	Solid radionuclide

Xoft again improperly attempts to limit a radiation source to a radionuclide. There are other sources of radiation besides radionuclides, and there is no basis in the intrinsic evidence for limiting the plain meaning of "radiation source" to a radionuclide. Moreover, Xoft neglects to define "solid," which refers to the fact that the radiation source that has a fixed shape and volume and is not deformable. (*See* AHC at 1295 ("of definite shape and volume; not liquid or gaseous"); Verhey Rep. at 11:8-9.)

U. "The Prescribed Absorbed Dose Is Delivered To The Target Tissue In Substantially Three Dimensions" (Claim 18)

Cytyc's Proposed Construction	Xoft's Proposed Construction
The prescribed absorbed dose is delivered to the target tissue such that all points at a given outward distance from the tissue wall will receive the same dose.	Prescribed absorbed dose is indefinite and substantially three dimensional is indefinite.

Contrary to Xoft's assertion, there is nothing indefinite about this limitation because one of ordinary skill in the art would understand what a prescribed absorbed dose is and how that dose can be delivered substantially in three dimensions. Dr. Verhey explains that this limitation relates to the fact that, once the outer chamber is expanded, the tissue in contact with the chamber conforms to the shape of the chamber, thereby assuring that all points within the tissue that are at a fixed distance from the wall of the surgical cavity will receive the identical dose. (Verhey Rep. at 11:12-15.) In this manner, the prescribed dose is delivered to the target tissue at the depth of interest substantially in all three dimensions, as opposed to being delivered in only two dimensions (to all points on a plane) or one dimension (to all points along a line). The limitation is clear, not indefinite, and should be given its ordinary meaning.

CONCLUSION

For the reasons stated above, this Court should adopt Cytyc's proposed constructions of the disputed terms of the '813 and '204 patents, and reject Xoft's proposed constructions and indefiniteness arguments.

Respectfully submitted,

DATED: November 9, 2006

HOWREY LLP

By: /s/ Henry C. Su
Henry C. Su

Attorneys for Defendants CYTYC CORPORATION and CYTYC SURGICAL PRODUCTS II, INC.

CERTIFICATE OF SERVICE

As required by Civil Local Rule 5-6(a)(2), the undersigned hereby certifies that on November 9, 2006, a true and correct copy of:

DEFENDANT AND COUNTERCLAIMANT CYTYC CORPORATION'S OPENING CLAIM CONSTRUCTION BRIEF (PAT. L.R. 4-5(a))

was served on the following counsel of record for Xoft, Inc. electronically through this Court's Electronic Case Filing System, in accordance with Civil Local Rule 5-5(b):

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Exhibit 9

APPLICATION

FOR

UNITED STATES LETTERS PATENT

Entitled

ASYMMETRIC RADIATION DOSING APPARATUS AND METHOD

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ABSTRACT OF THE DISCLOSURE

An interstitial brachytherapy apparatus of the invention delivers radioactive emissions in an asymmetric fashion to target tissue surrounding a surgical extraction site. The apparatus includes an expandable outer surface element defining an apparatus spatial volume, a radiation source disposed within the apparatus volume, and a means for providing predetermined asymmetric isodose curves within the target tissue. In one configuration, asymmetric isodose curves are created in the target tissue by shaping or locating the radiation source so as to be asymmetrically placed with respect to a longitudinal axis of the apparatus. In other configurations, asymmetric radiopaque shielding is provided between the radiation source and the target tissue. A surgical procedure using the apparatus is also described.

ASYMMETRIC RADIATION DOSING APPARATUS AND METHOD

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of co-pending U.S. Patent Application Serial No. 09/293,524, filed April 15, 1999, which is a continuation-in-part U.S. Patent Application Serial No. 08/900,021, filed July 24, 1997 (now issued as US 5,913,813 to Williams et al.); the contents of these applications are specifically incorporated herein by reference.

BACKGROUND OF THE INVENTION

The invention relates generally to an apparatus for use in treating proliferative tissue disorders, and more particularly to an apparatus for the treatment of such disorders in the body by the application of radiation.

Malignant tumors are often treated by surgical resection of the tumor to remove as much of the tumor as possible. Infiltration of the tumor cells into normal tissue surrounding the tumor, however, can limit the therapeutic value of surgical resection because the infiltration can be difficult or impossible to treat surgically. Radiation therapy can be used to supplement surgical resection by targeting the residual tumor margin after resection, with the goal of reducing its size or stabilizing it. Radiation therapy can be administered through one of several methods, or a combination of methods, including external-beam radiation, stereotactic radiosurgery, and permanent or temporary interstitial brachytherapy. The term "brachytherapy," as used herein, refers to radiation therapy delivered by a spatially confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site. Owing to the proximity of the radiation source, brachytherapy offers the advantage of delivering a more localized dose to the target tissue region.

For example, brachytherapy is performed by implanting radiation sources directly into the tissue to be treated. Brachytherapy is most appropriate where 1) malignant tumor regrowth occurs locally, within 2 or 3 cm of the original boundary of

the primary tumor site; 2) radiation therapy is a proven treatment for controlling the growth of the malignant tumor; and 3) there is a radiation dose-response relationship for the malignant tumor, but the dose that can be given safely with conventional external beam radiotherapy is limited by the tolerance or normal tissue. In brachytherapy, radiation doses are highest in close proximity to the radiotherapeutic source, providing a high tumor dose while sparing surrounding normal tissue. Interstitial brachytherapy is useful for treating malignant brain and breast tumors, among others.

Interstitial brachytherapy is traditionally carried out using radioactive seeds such as ^{125}I seeds. These seeds, however, produce inhomogeneous dose distributions. In order to achieve a minimum prescribed dosage throughout a target region of tissue, high activity seeds must be used, resulting in very high doses being delivered in some regions in proximity to the seed or seeds which can cause radionecrosis in healthy tissue. One attempt to address this problem, at least with respect to limiting dosages to critical organs near the radioactive seed site, has been to provide a shield directly on a portion of the seed or on an applicator that holds the seed to shield the particularly sensitive tissue. (E.g., Nath et al., Development of an ^{241}Am Applicator for Intracavitary Irradiation of Gynecologic Cancers, *Intl. J. Radiation Oncology Biol. Phys.*, Vol. 14, pp. 969-978.) While this approach may be appropriate for some applications, it may still be overly "hot" for treating proximate tissue on the unshielded side of the seed, while not providing an effective dose on the shielded side of the seed.

Williams U.S. patent no. 5,429,582, entitled "Tumor Treatment," describes a method and apparatus for treating tissue surrounding a surgically excised tumor with radioactive emissions to kill any cancer cells that may be present in the tissue surrounding the excised tumor. In order to implement the radioactive emissions, Williams provides a catheter having an inflatable balloon at its distal end that defines a distensible reservoir. Following surgical removal of a tumor, the surgeon introduces the balloon catheter into the surgically created pocket left following removal of the

tumor. The balloon is then inflated by injecting a fluid having one or more radionuclides into the distensible reservoir via a lumen in the catheter.

The apparatus described in Williams solves some of the problems found when using radioactive seeds for interstitial brachytherapy, but leaves some problems unresolved. The absorbed dose rate at a target point exterior to a radioactive source is inversely proportional to the square of the distance between the radiation source and the target point. As a result, where the radioactive source has sufficient activity to deliver a prescribed dose, say 2 centimeters into the target tissue, the tissue directly adjacent the wall of the distensible reservoir, where the distance to the radioactive source is very small, may still be overly "hot" to the point where healthy tissue necrosis may result. In general, the amount of radiation desired by the physician is a certain minimum amount that is delivered to a region up to about two centimeters away from the wall of the excised tumor. It is desirable to keep the radiation that is delivered to the tissue in the target treatment region within a narrow absorbed dose range to prevent over-exposure to tissue at or near the reservoir wall, while still delivering the minimum prescribed dose at the maximum prescribed distance from the reservoir wall. It is also desirable, at least in some applications, to provide these advantages while tailoring the radiation dosage to avoid fully dosing sensitive tissue or to reduce the amount of radiation that escapes the patient's body.

There is still a need for an instrument which can be used to deliver radiation from a radioactive source to target tissue within the human body with a desired intensity and at a predetermined distance from the radiation source without over-exposure of body tissues disposed between the radiation source and the target, and with the ability to shape the radiation dose to protect sensitive tissue or to protect against radiation exposure outside of the patient's body which may affect healthcare providers or others who might come close to the patient.

SUMMARY OF THE INVENTION

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The present invention solves the problems described above by providing an interstitial brachytherapy apparatus for delivering radioactive emissions in an asymmetric fashion to target tissue surrounding a surgical extraction site. The apparatus includes an expandable outer surface element defining an apparatus spatial volume, a radiation source disposed within the apparatus volume, and a means for providing predetermined asymmetric isodose profile within the target tissue.

In one configuration, asymmetric isodose curves are created in the target tissue by shaping or locating the radiation source so as to be asymmetrically placed with respect to a longitudinal axis of the apparatus. In one example of an apparatus having this configuration, an inner volume containing a liquid radioisotope is asymmetrically placed within the apparatus volume so as to result in an isodose profile in the target tissue that is asymmetric about the longitudinal axis of the apparatus.

In another example, the radiation source comprises a plurality of spaced apart solid radioactive particles disposed within the apparatus volume and arranged to provide a predetermined asymmetric isodose curve within the target tissue. In one particular example, the plurality of spaced apart radioactive particles are provided on a single elongate member that is shaped so that some of the radioactive particles are farther from the longitudinal axis of the apparatus than others. In other particular examples, a plurality of members carrying radioactive particles are provided with at least one of the members being shaped so as to place at least one radioactive particle asymmetrically with respect to the longitudinal axis of the apparatus.

An interstitial brachytherapy apparatus of the invention may also be implemented in a device having an expandable outer surface defining an apparatus volume, a radiation source disposed within and spaced apart from the expandable outer surface, and at least one asymmetric radiation shield spaced apart from the radiation source, the asymmetric radiation shielding resulting in predetermined asymmetric isodose curves within the target tissue. In one embodiment, radiopaque shielding is provided on a portion of the expandable outer surface. In another embodiment, the

radiation source is encompassed within a second, inner surface within the apparatus volume, with radiopaque shielding provided on at least a portion of the inner surface. In still further embodiments, one or more radiation shields are spaced apart from the radiation source and within the apparatus volume to achieve the desired asymmetric isodose distribution within the target tissue.

The invention also provides a method for treating a proliferating tissue disease using interstitial brachytherapy at an internal body location. The method includes surgically creating access to the proliferating tissue within a patient and surgically resecting at least a portion of the proliferating tissue to create a resection cavity within body tissue. An interstitial brachytherapy apparatus for delivering radioactive emissions as described above is then provided and intra-operatively placed into the resection cavity. After a prescribed absorbed dose has been delivered to tissue surrounding the apparatus, the apparatus is removed. The radioactive source material may be placed into the interstitial brachytherapy apparatus after the apparatus is placed in the resection cavity, and may be removed before the apparatus is removed. The method has particular applications to brain and breast cancers.

DESCRIPTION OF THE DRAWINGS

The foregoing features, objects and advantages of the invention will become apparent to those skilled in the art from the following detailed description of a preferred embodiment, especially when considered in conjunction with the accompanying drawings in which:

FIG. 1 is a side view of an interstitial brachytherapy apparatus of the invention for delivering asymmetric radioactive doses to body tissue;

FIG. 2 is a cross-sectional view taken along the line 2-2 in Figure 1;

FIG. 3 is a side view of an additional embodiment of an interstitial brachytherapy apparatus of the invention;

FIG. 3A is an end view of the interstitial brachytherapy apparatus of FIG. 3;

FIG. 4 is a side view of an additional embodiment of an interstitial brachytherapy apparatus of the invention;

FIG. 5 is a side view of an interstitial brachytherapy apparatus of the invention configured for use with a liquid radiation source.

FIG. 6 is a side view of an interstitial brachytherapy device of the invention employing radiopaque coatings;

FIG. 7 is a side view of an interstitial brachytherapy device of the invention employing radiopaque coating and a liquid radiation source; and

FIG. 8 and 9 are end views of interstitial brachytherapy devices of the invention employing radiopaque shields.

DESCRIPTION OF THE PREFERRED EMBODIMENT

A surgical instrument 10 for providing radiation treatment to proliferative tissue in a living patient is illustrated in FIG. 1. Surgical instrument 10 includes a tubular body member 12 having first and second lumens 14 and 16 (FIG. 2) extending from proximal ports 18 and 20 in a molded hub 22. The first lumen 14 carries a radioactive source 24 and second lumen 16 communicates with inflation port 26 formed through the side wall of the tube 12.

Affixed to the tubular body 12 proximate the distal end 28 thereof is an outer spatial volume 30 defined by an outer polymeric film barrier 32 that is appropriately spaced from the radioactive source 24. Outer volume 30 encompasses inflation port 26. With no limitation intended, the distensible polymeric film walls may comprise a biocompatible, radiation resistant polymer, such as silastic rubbers, polyurethanes, polyethylene, polypropylene, polyester, or PVC. The outer spatial volume 30 may be

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filled with air, saline or, alternatively, a radiation absorbing fluid, such as a contrast media used in angiography. Alternatively, the surface of outer volume 30 need not be a solid material. For example the surface of the outer volume 30 could be an expandable cage formed from a shape memory metal, such as nitinol, or a suitable plastic, such as an expandable polyethylene cage. Such a cage can be formed in the desired shape to conform to a particular isodose profile, contracted for delivery to the target site in vivo, then expanded to cause the tissue surrounding the surgically resected region to take the appropriate shape. The size of the outer spatial volume 30 generally will correspond approximately to the amount of tissue resected. For some applications, the size of the outer spatial volume 30 may be slightly smaller than the resected volume while for other applications, the outer spatial volume will be slightly larger than the resected volume, allowing the expandable surface of the outer spatial volume to urge tissue on the surface of the resected region into the appropriate shape to promote an even dose distribution around the outer spatial volume in the target tissue. In typical applications, the outer spatial volume has a diameter of approximately 2 to 6 centimeters.

Radiation source 24 comprises a wire 34 having one or more solid radioactive particles 36 located on the wire 34. For example, radioactive micro spheres of the type available from the 3M Company of St. Paul, Minnesota, may be used as the solid radioactive particles. Such a solid radioactive particle configuration offers an advantage in that it allows a wider range of radionuclides than if one is limited to liquids. Solid radionuclides that could be used with the delivery device of the present invention are currently generally available as brachytherapy radiation sources. Examples of radioactive materials which can be selected by a person of ordinary skills in the art for use with the present invention may be found in Tables 1 to 4 of PCT Publication WO 97/19723, which is hereby incorporated by reference.

The radioactive source 24 can either be preloaded into the catheter at the time of manufacture, or loaded into the device after it has been implanted into the space formerly occupied by the excised tumor. If loaded after implantation, the solid

radiation emitting material 36 can be inserted through lumen 14 on a wire 34, for example, using an afterloader (not shown).

Radiation source 24 has an asymmetric configuration with respect to a longitudinal axis 38 of the instrument 10. That is, radiation source 24 is shaped so as to result in an isodose profile 40 that varies radially about the longitudinal axis 38. More simply, the isodose profile 40 of FIG. 1 has a shorter radius from the longitudinal axis 38 on the top side of the instrument 10 as shown in FIG. 1 than on the bottom side. The asymmetrically shaped isodose curve 40 may be created by providing a plurality of solid radioactive particles 36 on a curved wire 34 in a spaced apart relationship. This configuration will result in certain of the solid radioactive particles 36 being farther from the longitudinal axis 38 of the instrument 10 than others, and will result in the illustrated asymmetric isodose profile 40. One way to provide the illustrated radioactive source 24 configuration is to form wire 34 from a solid or tubular shape memory alloy such as nickel-titanium alloys known in the art to have such properties. Wire 34 can then be preformed to the desired shape, can be compressed into a substantially straight configuration to pass through lumen 14, and will resume its desired shape once inside volume 30 where wire 34 will be free from steric constraints imposed inside the lumen 14. The resulting asymmetric isodose curve 40 can be further tailored by using solid radioactive particles 36 having differing specific activities to achieve the desired dosing.

In one embodiment, volume 30 and barrier 32 act to separate target tissue from the radiation source 24. Ideally, radiation therapy should make use the inherent difference in radiosensitivity between the tumor and the adjacent normal tissues to destroy cancerous tissue while causing minimal disruption to surrounding normal tissues. At high doses of radiation, however, the percentage of exposed cells that survive treatment decreases with first-order kinetics in proportion to increasing radiation dose. With increasing cell death comes increasing risk of necrosis or tissue death in healthy tissue that is treated with a high dose of radiation. Accordingly, it is desirable to keep the maximum radiation dose delivered by the brachytherapy apparatus

as low as possible while still delivering the desired therapeutic dose to the desired range of tissue. One method for achieving this result is to provide a "hotter" radiation source in a spaced apart relationship to the target tissue. In this way, because the intensity of the radiation emitted by a source drops with the square of the distance from the source, the effective dosage may be maintained below necrosis levels in target tissue closest to the interstitial brachytherapy apparatus while providing the required dosage to a greater depth into the target tissue. (See, e.g., U.S. Patent No. 5,913,813 which is hereby incorporated by reference in its entirety.) The capability of the apparatus of the invention to deliver absorbed doses deeper into the target tissue than prior interstitial brachytherapy devices while controlling the dose in proximity to the apparatus to reduce or eliminate the risk of healthy tissue necrosis allows for the use of brachytherapy in a greater number of cases.

For example, it is desirable to provide an interstitial brachytherapy device configured to provide a dose in a therapeutic range, say between 40 to 60 Gray, at a distance between 0.5 and 1.0 cm from the outer spatial volume for an outer spatial volume having a diameter of 4.0 cm and being in contact with the resection cavity wall. In a typical embodiment, the radioactive source material ranges from approximately 150 to 450 mCi in activity and encompasses most of the target treatment area with a 0.4 to 0.6 Gray/hour isodose contour. At this treatment rate, treatment may be completed in approximately 3 to 7 days, or more commonly, in approximately 3 to 5 days.

In some applications, the desired dosing profile is consistent with the shape of the outer volume 30. That is, the absorbed dose within the target tissue at points equidistant from the surface 32 of the outer spatial volume 30 should be substantially uniform in substantially every direction. Put another way, the three dimensional isodose profiles generated by the radiation source should be substantially similar in shape to the outer spatial volume 30. Where the apparatus of the invention is deployed in soft tissue, it may also be important for the surface 32 of the outer spatial volume 30 to be sufficiently firm so as to force the target tissue to take on the shape of the surface

30 so that the desired relationship between the isodose profiles and the target tissue is achieved.

While the interstitial brachytherapy device 10 of FIG. 1 may employ these techniques to positive effect, this device specifically alters the isodose profile for applications where particularly sensitive tissue or other concerns result in a desire to limit the dosage on one or more sides of the device as illustrated by isodose curve 40.

In a further embodiment of the brachytherapy device 50 of the invention, illustrated in FIG. 3, three solid radiation particles 52 are provided in a linear portion 54 of radiation source 56, while two additional radiation particles 52 are provided on co-planar extending portions 58, 60 of radiation source 56. An end view of the device 50 of FIG. 3 is shown in FIG. 3A with extending portions 58, 60 provided in a single plane 62 and resulting in isodose profile 64. A second inner, expandable surface 66 can also be provided within outer surface 68; the inner surface 66 enclosing the entirety of radiation source 56.

By providing extending portions 58, 60 having radioactive particles in the indicated co-planar relationship, areas of reduced dosage can be created on opposed sides of the device while maintaining symmetric dosing in all other directions. Of course, the number of sources and their configuration can be changed to create a desired asymmetric dosage. For example, an additional source could be added, for example above plane 62, to result in a symmetric isodose profile in all directions except the direction below the plane 62 which would have a lower dosage.

An additional device 80 of the invention, shown in FIG. 4, includes a radiation source 82 that is made up of three wires 84, 86, 88, each having a plurality of solid radiation particles. Wire 86 is a straight wire extending along the longitudinal axis 90 of the device, while wires 84, 88 each curve as wire 34 described above with respect to FIG. 1. Wires 84, 88 are coplanar, resulting in an isodose profile 92 that is similar to isodose profile 64 of FIG. 3A. That is, the isodose profile will be symmetric in the

plane in which the wires 84, 88 are disposed, but will have areas of reduced dosage in directions transverse to that plane (i.e., in Fig. 4, in the directions into and out of the page). As with the device 50 of FIGs. 3 and 3A, device 80 can be configured with more or fewer wires 84, 86, 88, and can be provided in configurations other than the depicted co-planar configuration in order to achieve desired asymmetric isodose profiles.

The asymmetric dosing effect achieved by the devices described above can also be achieved using a liquid radiation source. For example, device 100, illustrated in FIG. 5, has an outer surface 102 defining an outer volume 104 and an inner surface 106 defining an inner volume 108. The inner surface 106 is asymmetrically shaped or located with respect to the longitudinal axis 110 of the device 100 so as to result in the desired asymmetric dosing when the inner volume 108 is filled with a radioactive fluid. The inner volume 108 is spaced apart from the outer surface 102 and can be filled with a material containing a predetermined radionuclide, for example, I-125, I-131, Yb-169 or other source of radiation, such as radionuclides that emit photons, beta particles, gamma radiation, or other therapeutic rays. The radioactive material contained within the inner volume 108 can be a fluid made from any solution of radionuclide(s), e.g., a solution of Ir-192, I-125 or I-131. A radioactive fluid can also be produced using a slurry of a suitable fluid containing small particles of solid radionuclides, such as Au-198, Y-90. Moreover, the radionuclide(s) can be embodied in a gel. One radioactive material useful in the invention is Iotrex™, a sterile single use, non-pyrogenic solution containing sodium 3-(^{125}I)iodo-4-hydroxybenzenesulfonate (^{125}I-HBS), available from Proxima Therapeutics, Inc. of Alpharetta, Georgia. The inner volume 108 may be filled with radioactive fluid through port 112. Similarly, outer volume 104 can be filled on inflated using port 114.

A desired asymmetric dosing profile having the dosing characteristics described above may also be created by using asymmetric shielding between the radiation source and the target tissue as illustrated in FIGs. 6 through 9. In the device 120 of FIG. 6, a balloon 122 is located on the distal end of catheter 124. Radioactive particles 126 are

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disposed along the longitudinal axis 128 of the device. A portion of the surface, either inner or outer, of balloon 122 is coated with a radiopaque material 130 to result in asymmetric isodose curve 132. Radiopaque materials suitable for coating onto a polymeric surface of balloon 122 include, for example, barium, tungsten, bismuth, tantalum and tin.

A further device 140 having radiopaque shielding 142 is illustrated in FIG. 7. Device 140 includes an outer volume surface 144 and an inner volume surface 146. Inner surface 146 may contain a liquid radiation source, or may enclose one or more solid particles as used in device 120 (FIG. 6). In device 140, the radiopaque material 142 is coated onto a portion of either the inner or outer side of the inner volume surface 146, resulting in a desired asymmetric isodose profile 148.

Additional devices 160, 180 of the invention having radiation shielding 162 are illustrated in FIGs. 8 and 9, respectively. In these devices 160, 180, one or more radiation shields 162 are provided between and spaced apart from a radiation source (not shown) located along a longitudinal axis 164 of the device and the target tissue, which will be located outside of expandable surface 166. The radiation source can include a liquid or a solid radiation source as described above. Shields 162 can be formed from radiopaque materials including those described above with respect to the radiopaque coating and can extend longitudinally from a base on the device located within the expandable surface 166.

As shown in FIG. 8, device 160 has two radiation shields 162 on opposed sides of catheter 168. This configuration results in lower radiation dosing on the two sides of the device 160 on which the shields 162 are located as shown by isodose curve 170. Device 180 (FIG. 9) has a single radiation shield 162 resulting in an asymmetric isodose curve 182 as shown. A person or ordinary skill in the art will recognize that other configurations may be employed to achieve desired isodose curves.

The interstitial brachytherapy apparatus of the invention can be used in the treatment of a variety of malignant tumors, and is especially useful for in the treatment of brain and breast tumors.

Many breast cancer patients are candidates for breast conservation surgery, also known as lumpectomy, a procedure that is generally performed on early stage, smaller tumors. Breast conservation surgery is typically followed by postoperative radiation therapy. Studies report that 80% of breast cancer recurrences after conservation surgery occur near the original tumor site, strongly suggesting that a tumor bed "boost" of local radiation to administer a strong direct dose may be effective in killing any remaining cancer and preventing recurrence at the original site. The apparatus described herein can be used for either the primary or boost therapy. Numerous studies and clinical trials have established equivalence of survival for appropriate patients treated with conservation surgery plus radiation therapy compared to mastectomy.

Surgery and radiation therapy are also the standard treatments for malignant solid brain tumors. The goal of surgery is to remove as much of the tumor as possible without damaging vital brain tissue. The ability to remove the entire malignant tumor is limited by its tendency to infiltrate adjacent normal tissue. Partial removal reduces the amount of tumor to be treated by radiation therapy and, under some circumstances, helps to relieve symptoms by reducing pressure on the brain.

A method according to the invention for treating these and other malignancies begins by surgical resection of a tumor site to remove at least a portion of the cancerous tumor and create a resection cavity. Following tumor resection, but prior to closing the surgical site, the surgeon intra-operatively places an interstitial brachytherapy catheter apparatus, having an inner spatial volume and an outer spatial volume as described above but without having the radioactive source material loaded, into the tumor resection cavity. Once the patient has sufficiently recovered from the surgery, the interstitial brachytherapy catheter is loaded with a radiation source. The radioactive source dwells in the catheter until the prescribed dose of radiotherapy is delivered,

typically for approximately a week or less. The radiation source is then retrieved and the catheter is removed. The radiation treatment may end upon removal of the brachytherapy apparatus, or the brachytherapy may be supplemented by further doses of radiation supplied externally.

It will be understood that the foregoing is only illustrative of the principles of the invention, and that various modifications can be made by those skilled in the art without departing from the scope and spirit of the invention, including, but not limited to, combinations of elements from different embodiments found herein. All references cited herein are expressly incorporated by reference in their entirety.

What is claimed is:

1. An interstitial brachytherapy apparatus for treating target tissue surrounding a surgical extraction comprising:

an expandable outer surface defining an apparatus volume;

a radiation source replaceably disposable within the expandable outer surface, the radiation source comprising a plurality of solid radiation sources arranged to provide predetermined asymmetric isodose curves within the target tissue.

2. The apparatus of claim 1, wherein a plurality of solid radiation sources are provided in a spaced apart relationship on a single elongate member, the single elongate member being shaped to provide asymmetric placement of the spaced apart solid radiation sources with respect to a longitudinal axis through the apparatus volume.

3. The apparatus of claim 2, further comprising a catheter in communication with the apparatus volume, the elongate member extending through the catheter into the apparatus volume.

4. The apparatus of claim 3, wherein the elongate member is formed of a shape memory alloy, the elongate member being shaped to provide asymmetric placement of the spaced apart solid radiation sources, taking on a substantially straight shape while being inserted through the catheter to the apparatus volume, and resuming an asymmetric shape when extended into the apparatus volume.

5. The apparatus of claim 1, wherein at least one of the plurality of solid radiation sources has a different specific activity from at least one other solid radiation source.

6. The apparatus of claim 1, wherein the plurality of radiation sources are provided on at least two elongate members extending into the apparatus volume, at least one of the elongate members being shaped to provide asymmetric placement of a radiation source with respect to a longitudinal axis through the apparatus volume.

7. The apparatus of claim 6, wherein each of the at least two elongate members includes a plurality of solid radiation sources provided in a spaced apart relationship.

8. The apparatus of claim 1, wherein the expandable outer surface is sufficiently rigid to deform the target tissue into the shape of the expandable outer surface, causing the predetermined asymmetric isodose curves to penetrate into the target tissue to a prescribed depth.

9. An interstitial brachytherapy apparatus for treating target tissue surrounding a surgical extraction comprising:

an expandable outer surface having a base and defining an apparatus volume;

a radiation source replaceably disposable within and spaced apart from the expandable outer surface; and

an asymmetric radiation shield spaced apart from the radiation source, the asymmetric radiation shield providing predetermined asymmetric isodose curves within the target tissue.

10. The apparatus of claim 9, wherein the asymmetric radiation shield comprises a radio-opaque material disposed on a portion of the expandable outer surface.

11. The apparatus of claim 10, wherein the expandable outer surface comprises an inflatable balloon.

12. The apparatus of claim 11, wherein the radiation shield comprises a barium material disposed a portion of the inflatable balloon.

13. The apparatus of claim 9, further comprising at least one radiation shield extending from the base of the expandable outer surface toward an opposite end of the

expandable surface, the shield being in between and spaced apart from the radiation source and the expandable outer surface, the shield forming a radio-opaque barrier between a portion of the radiation source and the target tissue.

14. The apparatus of claim 13, wherein the radiation shield comprises two shields provided on opposite sides of the radiation source.

15. An interstitial brachytherapy apparatus for treating target tissue surrounding a surgical extraction comprising:

an expandable outer surface having a base and defining an apparatus volume;

a radiation source replaceably disposable within and spaced apart from the expandable outer surface; and

means for providing predetermined asymmetric isodose curves within the target tissue.

16. The apparatus of claim 15, wherein the means for providing predetermined asymmetric isodose curves within the target tissue comprises a plurality of solid radiation sources provided in a spaced apart relationship on an elongate member, the elongate member being shaped to provide asymmetric placement of the spaced apart solid radiation sources with respect to a longitudinal axis through the apparatus volume.

17. The apparatus of claim 15, wherein the means for providing predetermined asymmetric isodose curves within the target tissue comprises an asymmetric radiation shield spaced apart from the radiation source.

18. The apparatus of claim 17, wherein the radiation shield comprises two shields provided on opposite sides of the radiation source.

19. The apparatus of claim 15, wherein the expandable outer surface is sufficiently rigid to deform the target tissue into the shape of the expandable outer surface, causing the predetermined asymmetric isodose curves to penetrate into the target tissue to a prescribed depth.

Exhibit 10

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/464,727	12/16/99	WINKLER	

EXAMINER	
R	101360-16 (Q

ART UNIT	PAPER NUMBER
LACYK, J	5

021125
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QM22/1031

DATE MAILED:
3736

10/31/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95)

1- File Copy

Office Action Summary	Application No.	Applicant(s)	
	09/484,727	WINKLER ET AL.	
	Examiner	Art Unit	
	John P Lacyk	3736	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is FINAL. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-19 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-19 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2,4.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

U.S. Patent and Trademark Office
PTO-326 (Rev. 04-01) Office Action Summary Part of Paper No. 5

1. Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 2, line 1, "a plurality of solid radiation sources" should be –said plurality of solid radiation sources– .

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

3. Claims 1,9,15,17 are rejected under 35 U.S.C. 102(e) as being anticipated by McGrath et al.

McGrath et al discloses a device for treating tissue having an expandable outer surface and a radiation source disposed within the expandable surface having a plurality of solid radiation sources (Fig 2B). McGrath et al also teaches the use of shielding to absorb some of the radiation.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1, 8-15, 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ciezki et al (EP 0867200) in view of Apple et al (WO 99/33515)

Ciezki et al teaches a treatment device having a plurality of radiation sources disposed in a catheter. Ciezki et al also teaches the use of shielding or an attenuator made from a radio-opaque material i.e. tantalum. Ciezki et al teaches the claimed device except for the use of an inflatable balloon catheter or the specific use of barium as the shielding material. Apple et al teaches a radioactive treatment device that uses an inflatable balloon to place the catheter at the treatment site. Apple et al also teaches that it is well known to use a shielding made from any radio-opaque material, i.e. tantalum, barium, etc. Therefore a modification of Ciezki et al such that the catheter includes an inflatable balloon would have been obvious to help in the placement and retention of the cathether at the treatment site; further the modification such that the shielding material used is barium would have been obvious since Apple et al teaches that this is a well known material used in shielding radioactivity.

6. Claims 2-7, 16 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to John P Lacyk whose telephone number is 703-308-2995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-0758 for regular communications and 703-308-0758 for After Final communications.

8. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 308-0858.

John P Lacyk
Primary Examiner
Art Unit 3736

J.P. Lacyk
September 29, 2001